Strategies for managing sexual dysfunction induced by antidepressant medication (Review)

Taylor MJ, Rudkin L, Bullemor-Day P, Lubin J, Chukwujekwu C, Hawton K

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[Intervention Review]

Strategies for managing sexual dysfunction induced by antidepressant medication

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ABSTRACT

Background

Sexual dysfunction (including altered sexual desire, orgasmic and ejaculatory dysfunction, erectile and other problems) is a relatively common side effect of antidepressant medication. These sexual side effects may compromise a person's lifestyle and result in a lack of compliance with the prescribed antidepressant to the detriment of the person's mental health. A wide range of management strategies are possible to address this problem, including behavioural, psychological and pharmacological approaches.

Objectives

1. To determine the effectiveness of management strategies for sexual dysfunction caused by antidepressants.

2. To determine the adverse effects and acceptability of the different management strategies.

Search methods

We searched the Cochrane Depression, Anxiety and Neurosis Group's Specialized Register (CCDANCTR, to 1 January 2013), which includes relevant randomised controlled trials from the following bibliographic databases: The Cochrane Library (all years), EMBASE (1974 to date), MEDLINE (1950 to date) and PsycINFO (1967 to date). Additional searches were carried out by the author team on the same biomedical databases (using terms for 'sexual dysfunction' only) together with CINAHL (1982 to Jan 2012). The reference lists of reports of all included studies were screened.

Selection criteria

We included randomised controlled trials that compared management strategies for antidepressant-induced sexual dysfunction versus placebo or any alternative strategy.

Data collection and analysis

Two authors independently extracted data and assessed trial quality. Study authors were contacted for additional information.

Main results

We included 23 trials involving 1886 people in this updated review. Twenty-two of these trials investigated the addition of medication to treat the identified dysfunction, with most agents studied in only single studies. One study investigated switching to an alternative antidepressant.

In men, data for the phosphodiesterase inhibitors sildenafil (three studies, 255 participants) and tadalafil (one study, 54 participants) indicated they led to a greater improvement in erectile function than placebo. Combined data from three sildenafil studies found benefit over placebo on International Index of Erectile Function ratings of ability to achieve (MD 1.04, 95% CI 0.65 to 1.44), and maintain erections (MD 1.18, 95% CI 0.78 to 1.59). A single point improvement on these ratings is equivalent to an improvement in frequency from 'sometimes' to 'most times'. Men receiving tadalafil were more likely to report improved erectile function (RR 11.50, 95% CI 3.03 to 43.67). For women it remains uncertain whether sildenafil is more effective than placebo. Unpublished data could reduce this uncertainty.

Data from three studies in men and women of bupropion 150 mg twice daily indicate a benefit over placebo on rating scale scores (SMD 1.60, 95% CI 1.40 to 1.81), but response rates in two studies of bupropion 150 mg once daily demonstrated no statistically significant difference in effect (RR 0.62, 95% CI 0.09 to 4.41).

Other augmentation strategies failed to demonstrate significant improvements in sexual dysfunction compared with placebo.

One trial involving 75 people with sexual dysfunction due to sertraline assessed the effect of changing antidepressant. Switching to nefazodone was significantly less likely to result in the re-emergence of sexual dysfunction than restarting sertraline (RR 0.34, 95% CI 0.19 to 0.60), however, nefazodone is no longer available for clinical use.

There is an absence of randomised trials assessing the effects of switching to currently-available antidepressant agents with lower rates of adverse sexual effects, the role of psychological or mechanical interventions, or of techniques such as drug holidays.

We identified no data for any of the strategies included in the trials assessed that indicated that they led to a worsening of psychiatric symptoms. However, the relatively small numbers assessed for many of the interventions studied means that the possibility of such an effect cannot confidently be excluded in all cases.

Given the small numbers of studies assessing most of the strategies assessed, the presence of any unpublished trials could have substantial effects on estimates of effect. In some cases, only results from particular items or subscales within ratings scales are available. It is likely that this could act to bias estimates of effect obtained, increasing apparent effectiveness.

Authors' conclusions

The evidence currently available is rather limited. For men with antidepressant-induced erectile dysfunction, the addition of sildenafil or tadalafil appears to be an effective strategy. For women with antidepressant-induced sexual dysfunction the addition of bupropion at higher doses appears to be the most promising approach studied so far.

PLAIN LANGUAGE SUMMARY

Strategies for managing sexual dysfunction caused by antidepressants

Antidepressants can have numerous effects on sexual function including altered sexual desire, erection difficulties and orgasm problems. This systematic review investigated different ways to manage such sexual dysfunction. We included 23 randomised studies, with a total of 1886 participants who had developed their sexual problems while taking antidepressant medication. Twenty-two of these studies looked at the addition of further medication to the ongoing treatment for depression. For men with antidepressant-induced erectile dysfunction, the addition of sildenafil (Viagra; three studies, 255 participants) or tadalafil (Cialis; one study, 54 participants) appeared to improve the situation. For women with antidepressant-induced sexual dysfunction the addition of bupropion (Wellbutrin, Zyban; three studies, 482 participants) at higher doses appears to be the most promising approach studied so far, but further data from randomised trials are likely to be required before it can be recommended confidently. We did not find evidence that any intervention led to a worsening of psychiatric symptoms; however, we cannot be confident of this for many of the interventions studied, as only small numbers of participants have been studied so far.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Sildenafil compared with placebo for antidepressant-induced sexual dysfunction

Patient or population: people with antidepressant-induced sexual dysfunction
Settings: outpatient
Intervention: sildenafil
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (no of studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Sildenafil				
Endpoint International Index of Erectile Function (IIEF) total scores (The IIEF is a self-report measure with 15 questions examining erectile function, orgasmic function, sexual desire, and intercourse satisfaction. Maximum possible score 75)	The mean IIEF score ranged across control groups from 40.9 to 44.2	The mean IIEF score in the intervention groups was 19.36 higher (15.00 to 23.72 higher)		112 men (2 studies)	⊕⊕⊕⊕ **high**	
Endpoint International Index of Erectile Function (IIEF) scores - question 3: ability to achieve erection (Maximum score 5)	The mean score in control groups was 3.1	The mean score in the intervention groups was 1.04 higher (0.65 to 1.44 higher)		231 men (2 studies)	⊕⊕⊕⊕ **high**	

Endpoint International Index of Erectile Function (IIEF) scores - intercourse satisfaction (questions 6, 7, 8) (Maximum score 15)	The mean score in the control group was 7.2	The mean score in the intervention group was 3.50 higher (2.48 to 4.52 higher)		89 men (1 study)	⊕⊕⊕○ **moderate**
Clinical Global Impression -Sexual Function not ‘ ‘ much/very much improved” by endpoint	**Male population**		**RR** 0.44 (0.33 to 0.58)	187 (2 studies)	⊕⊕⊕○ **moderate**
	956 per 1000	**459 per 1000** (325 to 630)			
	Female population				
	735 per 1000	**287 per 1000** (176 to 456)			
Dropouts (People leaving the trial early)	**Low risk population**		**RR** 0.68 (0.41 to 1.14)	353 (4 studies)	⊕⊕⊕⊕ **high**
	90 per 1000	**61 per 1000** (37 to 103)			
	Medium risk population				
	250 per 1000	**170 per 1000** (102 to 285)			
	High risk population				
	360 per 1000	**245 per 1000** (148 to 411)			
Global Efficacy Questionnaire (questions 1 & 2) (Questions assessing improvement attributed to	**Improvement in erections**		**RR** 2.50 (1.67 to 3.73) and **RR** 2.55 (1.71 to 3.80)	284 men (1 study)	⊕⊕⊕○ **moderate**

medication compared to having no treatment at all)			
	282 per 1000	**705 per 1000** (470 to 1000)	
	Improvement in ability to have sexual intercourse		
	282 per 1000	**719 per 1000** (482 to 1000)	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk Ratio

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

The evidence for effects based on single trials is rated as moderate quality since further trial data may well change the estimate.

BACKGROUND

Description of the condition

Antidepressant medications are widely prescribed (Donoghue 1996; Jick 1995; Moore 2009). Sexual dysfunction is a common, well-known adverse effect of all antidepressants (Balon 1993; Baldwin 1997; Williams 2006; Williams 2010). These sexual adverse effects can affect a person's lifestyle considerably, and, where this results in reduced compliance with medication, lead to less effective treatment of the primary psychiatric disorder.

Several different types of sexual dysfunction may be related to antidepressants, including altered sexual desire - such as loss or lack of desire; orgasmic and ejaculatory dysfunction, including anorgasmia (inability to achieve orgasm), hyperorgasmia (significantly more orgasms in a short time period than normal), painful orgasm and inhibited ejaculation; erectile problems, including erectile dysfunction (impotence), priapism (significantly prolonged erection) and painful erection - and other issues, including problems of sexual arousal, reduced sexual satisfaction, lubrication, dyspareunia (painful intercourse) and vaginismus (tensing of vaginal muscles that make intercourse painful or impossible).

Identifying antidepressant-induced sexual dysfunction can be complicated by the association of sexual dysfunction with some disorders that antidepressants are used to treat. For example, depression is associated with increased rates of reported sexual dysfunction even when no treatment is received (Angst 1998).

Sexual dysfunction has been reported with all classes of antidepressant medication. Reported rates of sexual dysfunction are typically underestimates, as sexual adverse effects are often not specifically asked about in treatment trials, while direct questioning can reveal higher rates than are reported spontaneously (Montejo-Gonzalez 1997). Studies of the prevalence of antidepressant-induced sexual dysfunction have exhibited a number of methodological problems (Montgomery 2002). These include the frequent absence of comparison groups or baseline assessments, and inconsistent definitions of sexual dysfunction between studies.

The majority of studies directly comparing rates of sexual dysfunction between different antidepressants have involved selective serotonin reuptake inhibitors (SSRIs). Generally, trials have reported no significant differences between these drugs in rates of sexual dysfunction, with sexual dysfunction reported in population surveys by over one third of participants (Williams 2006; Williams 2010). In randomised trials, nefazodone (a serotonin antagonist and reuptake inhibitor) and bupropion (a norepinephrine-dopamine reuptake inhibitor) have been associated with less sexual dysfunction than the SSRI, sertraline (Croft 1999; Feiger 1996), and reboxetine (a norepinephrine reuptake inhibitor) with greater sexual satisfaction than the SSRI fluoxetine (Clayton 2003). The monoamine oxidase inhibitor, moclobemide, was more commonly associated with increased sexual desire than the tricyclic antidepressant, doxepin (Philipp 1993). Further information on rates of sexual dysfunction with antidepressants can be found elsewhere (Gregorian 2002; Montgomery 2002; Serretti 2009).

Description of the intervention

Management strategies described for the treatment of antidepressant-induced sexual dysfunction include waiting for the problem to resolve; behavioural strategies modifying sexual technique; individual and couple psychotherapy; alterations of antidepressant usage, including reducing dose; delaying use until after sexual activity; 'drug holidays'; switching to a different antidepressant; and the use of additional agents (Baldwin 2004). A wide range of additional agents have been employed clinically to try to reverse this problem, for example erectile dysfunction might be treated with a phosphodiesterase inhibitor such as sildenafil or tadalafil. However, additional treatments may themselves have adverse effects and tolerability problems, and could, in theory, affect the primary psychiatric condition for which the antidepressants were prescribed.

How the intervention might work

The mechanisms by which antidepressants cause sexual dysfunction involve complex multi-system interactions, which are not entirely understood. Psychological factors such as anxiety may also play a role in maintaining dysfunction. The main neurotransmitters involved are serotonin (5HT), acetylcholine, noradrenaline, and dopamine. The adverse sexual effects may be caused centrally or peripherally and may result from the change in function of one or more neurotransmitter. Given this complex system, additional treatments employed have had a wide variety of putative mechanisms. Such treatments have included sildenafil (a phosphodiesterase inhibitor), amantadine (a dopamine agonist), cyproheptadine (an antihistamine and 5HT blocker), yohimbine (an alpha-2 blocker), buspirone (a 5HT1A receptor agonist), bethanechol (an acetylcholine agonist) and *Ginkgo biloba* (a herbal medication).

Why it is important to do this review

This is an update of a Cochrane review first published in 2004. That review noted that the available evidence was rather limited, with small numbers of trials assessing each strategy. This review aims to summarise the current evidence regarding potential strategies for managing antidepressant-induced sexual dysfunction, noting how well the sexual dysfunction responds, as well as risks, such as adverse effects or worsening of the condition for which the antidepressant was initially prescribed. This should assist patients and their clinicians when deciding how best to manage these common problems.

Attention is drawn to the related Cochrane review on the management of sexual dysfunction due to antipsychotic drug therapy (Berner 2007; Schmidt 2012).

OBJECTIVES

1. To determine the effectiveness of management strategies for sexual dysfunction caused by antidepressants.

2. To determine the adverse effects and acceptability of the different management strategies.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials in the review. Cluster randomised trials and trials of both parallel group and cross-over design were considered suitable for inclusion.Trials using non-randomised allocation were not included, in order to reduce risks of selection and publication bias (Alderson 2004).

Types of participants

Patients aged 16 years and over with sexual dysfunction (including, but not restricted to altered sexual desire, orgasmic and ejaculatory dysfunction, erectile problems, problems of sexual arousal, reduced sexual satisfaction, lubrication, dyspareunia and vaginismus).as a result of being treated with an antidepressant (except mood stabilisers) on any dose regime.
Participants from inpatient or community settings were eligible for inclusion.
Inclusion was not restricted on the basis of the disorder for which the antidepressant had been prescribed.

Types of interventions

Experimental intervention

Any management strategy - pharmacological, psychological or otherwise - for antidepressant-induced sexual dysfunction.

Comparator intervention

Placebo or any alternative strategy.

Types of outcome measures

Primary outcomes

1. Changes, or post-treatment differences, in the severity of the identified sexual dysfunction (assessed by self (self-rated measures) or interviewer (interviewer-rated measures), or both.

Secondary outcomes

2. Changes, or post-treatment differences, in sexual satisfaction and functioning (based on self- or interviewer-rated measures, or both).
3. Dropout rates as a measure of the acceptability of specific therapies.
4. Change, or post-treatment differences, in the primary psychiatric condition for which the antidepressant was being prescribed (based on symptom ratings).
Outcomes at trial endpoint were employed, where available. No decision was made to favour self-reported or interviewer-rated measures.

Search methods for identification of studies

CCDAN's Specialized Register (CCDANCTR)

The Cochrane Depression, Anxiety and Neurosis Group (CCDAN) maintains two clinical trials registers at the editorial base (Bristol, UK), a references register and a studies-based register. The CCDANCTR-References Register contains over 29,500 reports of randomised controlled trials in depression, anxiety and neurosis. Approximately 65% of these references have been tagged to individual, coded trials. The coded trials are held in the CCDANCTR-Studies Register and records are linked between the two registers through the use of unique Study ID tags. Coding of trials is based on the EU-Psi coding manual. Please contact the CCDAN Trials Search Co-ordinator for further details. Reports of trials for inclusion in the Group's registers are collated from routine (weekly), generic searches of MEDLINE (1950 to date), EMBASE (1974 to date) and PsycINFO (1967 to date); quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL) and review-specific searches of additional databases. Reports of trials are also sourced from international trials registers c/o the World Health Organization's trials portal (ICTRP), drug companies, the handsearching of key journals, conference proceedings and other (non-Cochrane) systematic reviews and meta-analyses. Details of CCDAN's generic search strategies can be found on the Group's website.

Electronic searches

Electronic searches included:
1. The CCDANCTR-Studies Register (all years to 1 August 2012, with a further update search for 1 January 2013), using the following coding terms:
Condition = ("sexual dysfunction*" and "drug induced") or Comorbidity = ("sexual dysfunction*").
2. The CCDANCTR-References Register, using a more sensitive set of free-text terms to find additional untagged/uncoded references (Appendix 1).
3. Independent searches by the author team on the Cochrane Register of Controlled Trials (CENTRAL) (2012, Issue 1), CINAHL (1982 to 12 January 2012), EMBASE (1980 to 12 January 2012), MEDLINE (1966 to 12 January 2012) and PsycINFO (1984 to 12 January 2012) (Appendix 2).
4. International trials registries (ClinicalTrials.gov and ICTRP, 1 January 2013), to identify additional ongoing or unpublished studies .

Searching other resources

Reference checking

The reference lists of all trials identified for inclusion were examined, together with other articles on adverse sexual effects of antidepressants, and relevant conference proceedings.

Personal communications

The following experts in the field of sexology were contacted for the original review: J Bancroft, R Basson, J Heiman and R Rosen.

Pharmaceutical companies

For the original review, the authors contacted pharmaceutical companies manufacturing antidepressant medication to find out if they knew of any published or unpublished studies relevant to this review. This search was not repeated for the update.

Data collection and analysis

Selection of studies

Trial inclusion or exclusion was determined independently by two authors. Full reports of studies were used for this assessment, except where a trial could be excluded on the basis of title and abstract alone. Any disagreements were resolved by consensus discussion with a third member of the review team.

Data extraction and management

Data were extracted from the included studies about participants' characteristics, intervention details (including whether or not the study was of a discontinuation design) and outcome measures. The data were extracted independently by two authors. Where inadequate trial data were provided, the authors were contacted in order to obtain further information. Where standard deviations were not reported but could be calculated from standard errors this was done in conventional fashion (Cochrane Handbook chapter 7.7.3.3 Higgins 2009). Any disagreements were resolved by consensus discussion with a third member of the review team.

Main planned comparisons

We planned to compare each experimental intervention with placebo or alternative comparator intervention, and, where possible, to group comparisons of interventions with similar mechanisms.

Assessment of risk of bias in included studies

Two authors independently assessed the methodological quality of the included studies using the Cochrane Collaboration tool for risk of bias (Higgins 2011). Any disagreements were resolved by consensus discussion with a third member of the review team. The risk of bias tool assesses seven domains namely: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and 'other issues'. Each domain is assigned one of the following judgements: 'low risk' of bias, 'high risk' of bias, or 'unclear risk' of bias, and a supporting statement is provided to back up the judgement.

Measures of treatment effect

Data were analysed using Review Manager software (version 5.2). For binary efficacy outcomes, a pooled risk ratio (with 95% confidence intervals) was calculated using a fixed-effect model. Risk ratios are reported since this measure can be more readily applied in clinical practice (Sackett 1996; Sinclair 1994). For continuously distributed outcomes, the mean difference (MD) was calculated when the same scale was used by all studies. Standardised mean difference was employed for comparisons across different scales.
We extracted outcome data collected from any time point, but our reported analyses use trial endpoint data, except where specified. Differences between trials in the times of assessment are reported.

Unit of analysis issues

Cluster-randomised trials

The review protocol did not address how we would include data from cluster-randomised trials. Although none have been encountered in this review, the appropriate methods, should they need to be included, will be included in a future update of this review.

Cross-over trials

We intended to use data from the first period of treatment only for cross-over trials, but we did use pooled data from both periods where these were the only data available.

Studies with multiple treatment groups

Where studies included multiple treatment groups, pair-wise comparisons are reported. This may lead to increased correlation between estimated intervention effects across such comparisons, as described in the Cochrane Handbook. Where possible, groups were combined to create a single pair-wise comparison or alternatively the 'shared' control group data were split into two or more groups with smaller sample size(s).

Dealing with missing data

We used trial data from intention-to-treat analyses when available. Where this was not possible, we used endpoint data for the participants who completed the trial. Where necessary, we wrote to study authors to request missing data.

Assessment of heterogeneity

Statistical heterogeneity between studies was assessed using the I^2 statistic. The Cochrane Handbook suggests interpretation of an I^2 of 0% to 40% as being potentially unimportant heterogeneity, 30% to 60% as representing moderate heterogeneity, 50% to 90% indicating substantial heterogeneity, and 75% to 100% indicating considerable heterogeneity (Higgins 2003).

Assessment of reporting biases

We considered methods to look for evidence of small study bias, but the number of trials identified for each comparison was too limited for this to be appropriate. Should the number of trials available increase in future updates of this review, the use of methods such as funnel plots and statistical tests to identify possible publication bias will be considered.

Data synthesis

Fixed-effect analyses are presented unless otherwise stated. Random-effects models were used routinely to investigate the sensitivity of results to the choice of statistical method, but we observed no cases where this altered estimates of effect qualitatively.

Subgroup analysis and investigation of heterogeneity

Subgroup analyses were planned by:
1. Gender of those experiencing sexual dysfunction (men only, women only, mixed group).
2. Dose of intervention.

Sensitivity analysis

Possible sensitivity analyses were considered to assess the impact of differences in study methodology on outcomes, but no such analyses were performed in view of the small numbers of trials identified for each intervention.

'Summary of findings' table

As this review addresses more than one major treatment comparison, separate 'Summary of findings' tables were prepared for interventions where data were available from three or more trials. Outcome data were summarised separately by gender, where possible. Assumed baseline risks were taken from median control group risks across included studies. Quality of evidence used was assessed using the specific evidence grading system developed by the GRADE working group (GRADE working group 2004).

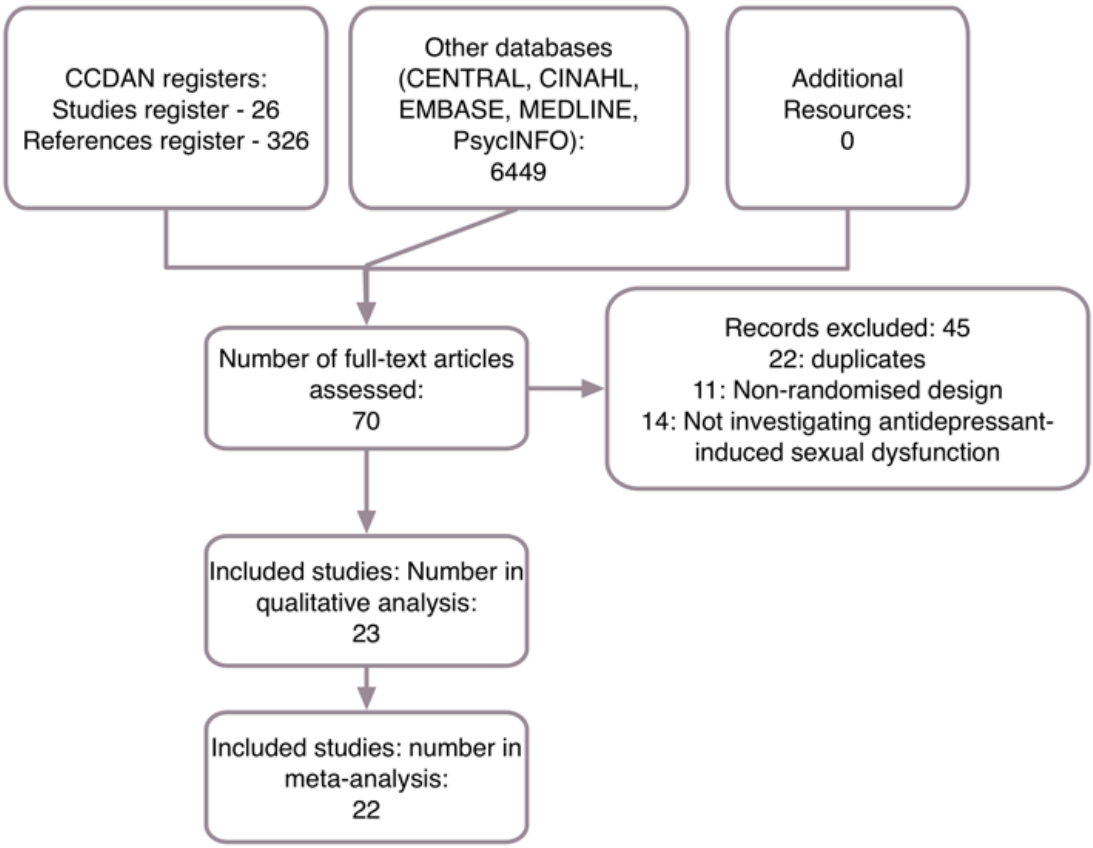
RESULTS

Description of studies

Results of the search

Over 6000 citations were identified by the search strategy of this review (Figure 1). Of these, 70 citations appeared potentially relevant and 23 were included, 22 of which provided data for quantitative analysis.

Figure 1. Study flow diagram



Further information was provided by the authors of several studies (Clayton 2004; Ferguson 2001; Ginsberg 2001; Jacobsen 1996; Michelson 2002; Nurnberg 2003).

Included studies

Design

We identified 23 studies that met the inclusion criteria for this review (see Characteristics of included studies). Some additional studies were identified too late for inclusion in this version of the review, and so are awaiting classification (see Characteristics of studies awaiting classification). If suitable, they will be included in a future update of the review.

Nineteen studies were of parallel-group design, and three used a cross-over design (Bernik 2004; Meston 2004; Nelson 2001). Length of included trials ranged from 14 days to 26 weeks. Where trials described a period of randomised treatment followed by a non-randomised period, we have reported only the period of randomised treatment.

Sample sizes

Numbers of people randomised within individual studies varied greatly from 12 participants (Bernik 2004; Jespersen 2004), to 288 (Baldwin 2008). This update adds new data from several studies with over 100 participants (Baldwin 2008; Fava 2006; Safarinejad 2010; Safarinejad 2011).

Setting

Participants were recruited to studies taking place in a range of countries. The greatest number of studies took place in the USA and Europe, but studies were identified from South Korea (Kang 2002), and South Africa (Jespersen 2004), with two large new studies from Iran (Safarinejad 2010, Safarinejad 2011).

Participants

The total number of participants randomised in the 23 studies was 1886.

Participants in 12 of the studies had developed adverse sexual effects from the use of a selective serotonin reuptake inhibitor (SSRI). Two participants in one study had received nortriptyline, a tricyclic antidepressant (Kang 2002). One study did not specify the type of antidepressant involved (Jespersen 2004).

Seven studies included only women (Jespersen 2004; Meston 2004; Michelson 2000; Michelson 2002; Nurnberg 2002; Nurnberg 2008; Safarinejad 2011), and four studies included only men (Fava 2006; Ginsberg 2001; Nurnberg 2003; Safarinejad 2010). One study did not describe the gender of those participating (Masand 2001), and the remaining studies recruited both men and women.

The participants in studies had wholly, or partially, recovered from the disorder for which antidepressants had been prescribed - most commonly depression (see Characteristics of included studies). Two studies reported inclusion of mood and anxiety disorders (Ginsberg 2001; Kang 2002), and one study included participants treated for depression, bipolar disorder and obsessive compulsive disorder (Jacobsen 1996). One study was restricted to people treated for panic disorder (Bernik 2004).

While most studies did not restrict inclusion to particular types of sexual dysfunction, one study employing sildenafil restricted inclusion to antidepressant-induced erectile dysfunction (Fava 2006), and another investigating bethanecol limited inclusion to ejaculatory delay or anorgasmia (Bernik 2004).

Interventions

The range of intervention types assessed was limited and is outlined below.

Addition of further medication

The majority of studies assessed the addition of further medication to ongoing antidepressant treatment using a placebo control. Two studies had more than one active treatment arm in addition to the placebo arm of the trial (Michelson 2000; Michelson 2002).

The interventions for which the greatest number of studies were identified were bupropion and sildenafil.

Sildenafil, a phosphodiesterase inhibitor, was investigated in five trials with a total of 503 participants (Fava 2006; Ginsberg 2001; Nurnberg 2002; Nurnberg 2003; Nurnberg 2008). The range of doses taken once daily varied between 25 mg and 100 mg in one study (Fava 2006), and a dose between 50 mg and 100mg was employed in the remaining four studies (Ginsberg 2001; Nurnberg 2002; Nurnberg 2003; Nurnberg 2008).

Bupropion, which is thought to act by dual noradrenaline and dopamine reuptake inhibition (Stahl 2004), was investigated in five trials with a total of 579 participants (Clayton 2004; DeBattista 2005; Masand 2001; Safarinejad 2010; Safarinejad 2011). Bupropion (sustained release) was prescribed at a dose of 150 mg daily in two studies (DeBattista 2005; Masand 2001), and at 150 mg twice daily in the remaining studies (Clayton 2004; Safarinejad 2010; Safarinejad 2011).

A wide range of other agents were investigated in fewer studies including:

1. A second phosphodiesterase inhibitor, tadalafil (in doses of 10 mg or 20 mg), tested in one study with 54 participants (Evliyaoğ lu 2011).
2. Two 5HT1A receptor agonists: VML-670, a 5-HT1A receptor agonist (300 μg once daily) tested in a study with 288 participants (Baldwin 2008), and buspirone, another 5-HT1A receptor agonist (30 mg daily), tested in a study with 61 participants (Michelson 2000); the Michelson 2000 study also included an active treatment as the comparison treatment, amantadine, a dopaminergic agent (50 mg twice daily).
3. A herbal extract of *Ginkgo biloba:* two studies with 61 participants tested a herbal extract of *Ginkgo biloba* (240 mg daily) (Kang 2002; Wheatley 2004).
4. Granisetron, a 5-HT3 antagonist, was investigated in two studies with 32 participants (Jespersen 2004; Nelson 2001). Nelson 2001 used a dose of 1 mg to 2 mg, but the dosage was not specified in the other study.
5. Bethanecol (20 mg), an agent with mixed cholinergic and adrenergic effects, investigated in one study with 12 participants (Bernik 2004).
6. Two 5HT2 receptor antagonists, olanzapine (2.5 mg daily) and mirtazapine (15 mg daily) were investigated in the same four-arm study (Michelson 2002). This study also included an active treatment comparison with yohimbine, an alpha-2 adrenoceptor antagonist (5.4 mg daily). Yohimbine was also studied at a dose of 5.4 mg three times daily in a another trial with 33 participants (Jacobsen 1996).
7. Ephedrine was investigated in one study (Meston 2004).
8. Two different doses of maca root extract were compared in one study (Dording 2008).

Change in antidepressant prescription

One study assessed changing from an SSRI to an antidepressant, nefazodone, with a different mode of action (Ferguson 2001).

Other approaches

No studies were identified that assessed the use of drug holidays, psychological interventions, or mechanical devices to treat sexual dysfunction.

Outcomes

1) Measures of sexual function, dysfunction and satisfaction

The trials used a variety of outcome measures to assess initial sexual function and response to treatment. These included both self-assessment and externally-rated measures. The scales used included:

1. International Index of Erectile Function (IIEF; Rosen 1997).
2. Arizona Sexual Experiences Scale (ASEX; McGahuey 2000).
3. Changes in Sexual Functioning Questionnaire (CSFQ; Clayton 1997).
4. Erectile Dysfunction Inventory of Treatment Satisfaction (EDITS; Althof 1999).
5. General Assessment Questions (GAQ; Evliyaoğlu 2011).
6. Sexual Side Effects Scale (SSES; Nelson 2001).
7. Brief Index of Sexual Functioning for Women (BISF-W; Taylor 1994).
8. Feiger Sexual Function and Satisfaction Questionnaire (FSFSQ; Feiger 1996).
9. Udvalg fur Kliniske Undersogelser side effect rating scale (UKU; Lingjaerde 1987).
10. Massachussetts General Hospital-Sexual Functioning Questionnaire (MGH-SFQ; Labbate 2001).
11. Clinical Global Impression Scale adapted for Sexual Function (CGI-SF; Guy 1976).
12. The Physician's Rating of Sexual Dysfunction Symptoms (PRSDS; Ferguson 2001).
13. A modified version of the Rush-Presbyterian Sexual Function Inventory (R-SFI; Ferguson 2001).
14. Interviewer Rating of Sexual Dysfunction, a semi-structured interview (Michelson 2000).
15. Visual analogue scales (Bernik 2004; Michelson 2000).
16. Investigator-devised measures (Kang 2002; Wheatley 2004).

2) Measures of psychiatric symptoms

Depressive symptoms were measured using the Hamilton Rating Scale for Depression (HAM-D; Hamilton 1960), Clinical Global Impression, and Beck Depression Inventory (Beck 1961). Anxiety symptoms were measured using the Hamilton Rating Scale for Anxiety (HAM-A; Hamilton 1959), and the State-Trait Anxiety Inventory (Spielberger 1983).

Excluded studies

A number of studies were excluded from the review (see Characteristics of excluded studies). The most common reason for exclusion was that randomised allocation was not employed, or it was not established that the sexual dysfunction was attributable to use of antidepressants.

Ongoing studies

Six studies were identified that are ongoing, or yet to report (see Characteristics of ongoing studies). It appears, from published trial registers, that one ongoing study is investigating change of antidepressant (Takeda 2011). The remaining studies are investigating trazodone (Chiang 2010), ropinirole (Hellerstein 2008), maca root (Dording 2010), combinations of testosterone with sildenafil or buspirone (Van Rooiji 2010), and *Ginkgo biloba*, sex therapy, and a combination of the two (Meston 2008).

Studies awaiting classification

Four studies are awaiting classification (see Characteristics of studies awaiting classification), and, if suitable, will be included in future updates of this review.

New studies found at this update

The original version of this review included 15 studies with around 900 participants. The current version includes 23 studies with 1886 participants, so there has been a substantial increase in the availability of data from randomised trials to address this area of interest.

Risk of bias in included studies

Risk of bias judgements are presented graphically in Figure 2 and Figure 3 with further details tabulated in the Characteristics of included studies table.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

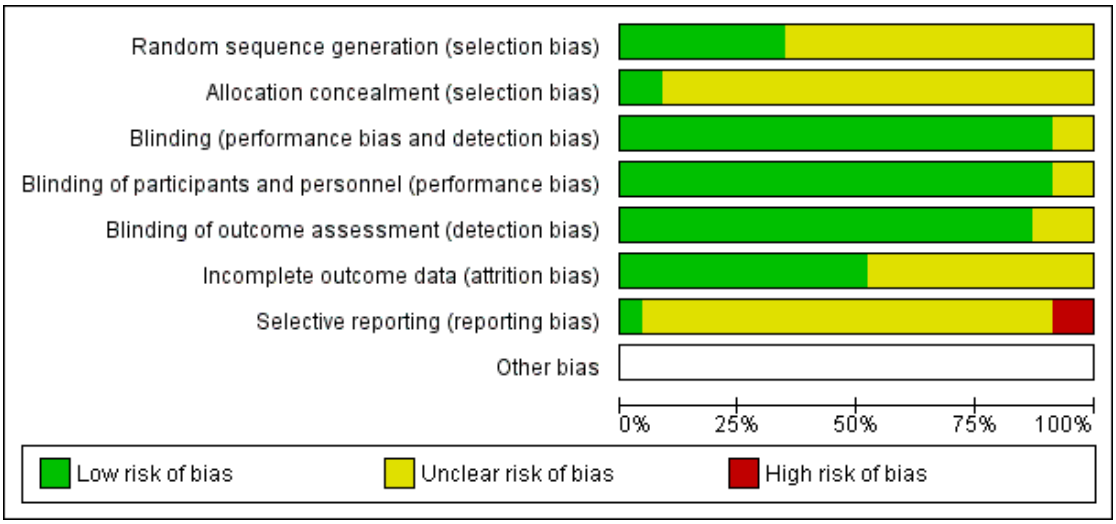
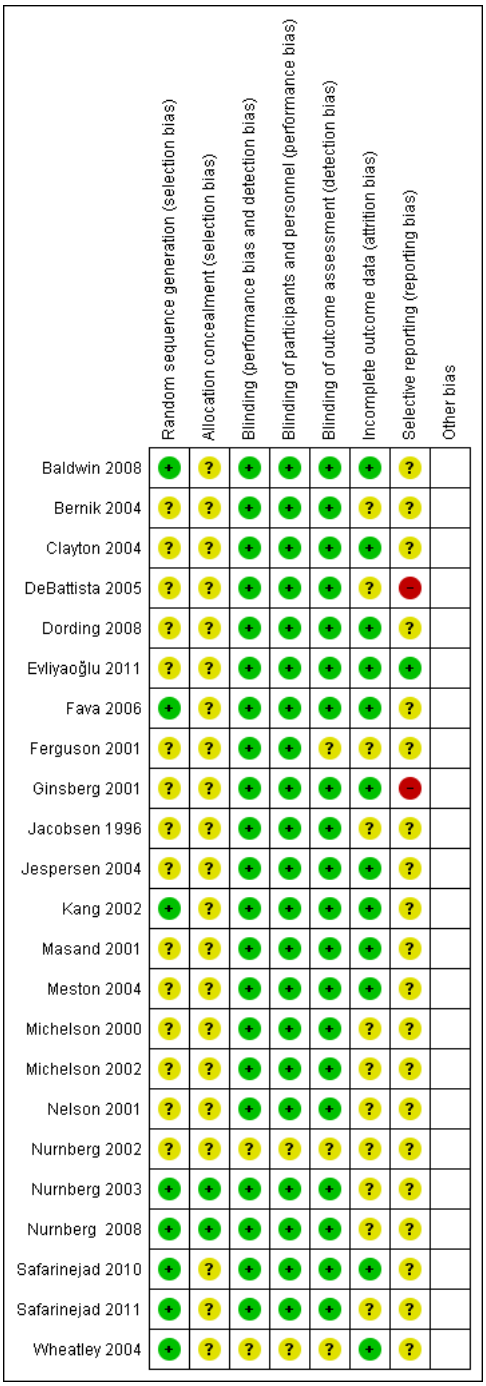


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

There was generally little information provided on methods used for randomisation or used to maintain concealment of allocation.

Blinding

While most studies reported use of blinding, commonly a 'double-blind' design (Figure 2), the extent of blinding was well described in a minority of studies. Meston 2004 described testing participant blinding for effectiveness, and finding that nine out of 11 women correctly identified the order of treatment received.

Incomplete outcome data

The majority of included studies did not include, or did not report, inclusion of withdrawals or dropouts in analyses. Four of the studies specified that they included withdrawals and dropouts in analyses by carrying forward prior observations (Ferguson 2001; Ginsberg 2001; Michelson 2002; Nurnberg 2003). None followed up withdrawals to obtain further outcome data. The data currently available on dropout rates for Ginsberg 2001 refer to the total over both the initial placebo-controlled period, and the second stage of the trial in which all participants received sildenafil.

Selective reporting

It was unclear in the majority of studies whether there had been selective reporting of data, since original study protocols were not available. In some cases, only data from particular subscales or questions within a larger scale were reported.

Effects of interventions

See: **Summary of findings for the main comparison** Sildenafil versus placebo; **Summary of findings 2** Bupropion versus placebo

Comparison one: Addition of phosphodiesterase inhibitor

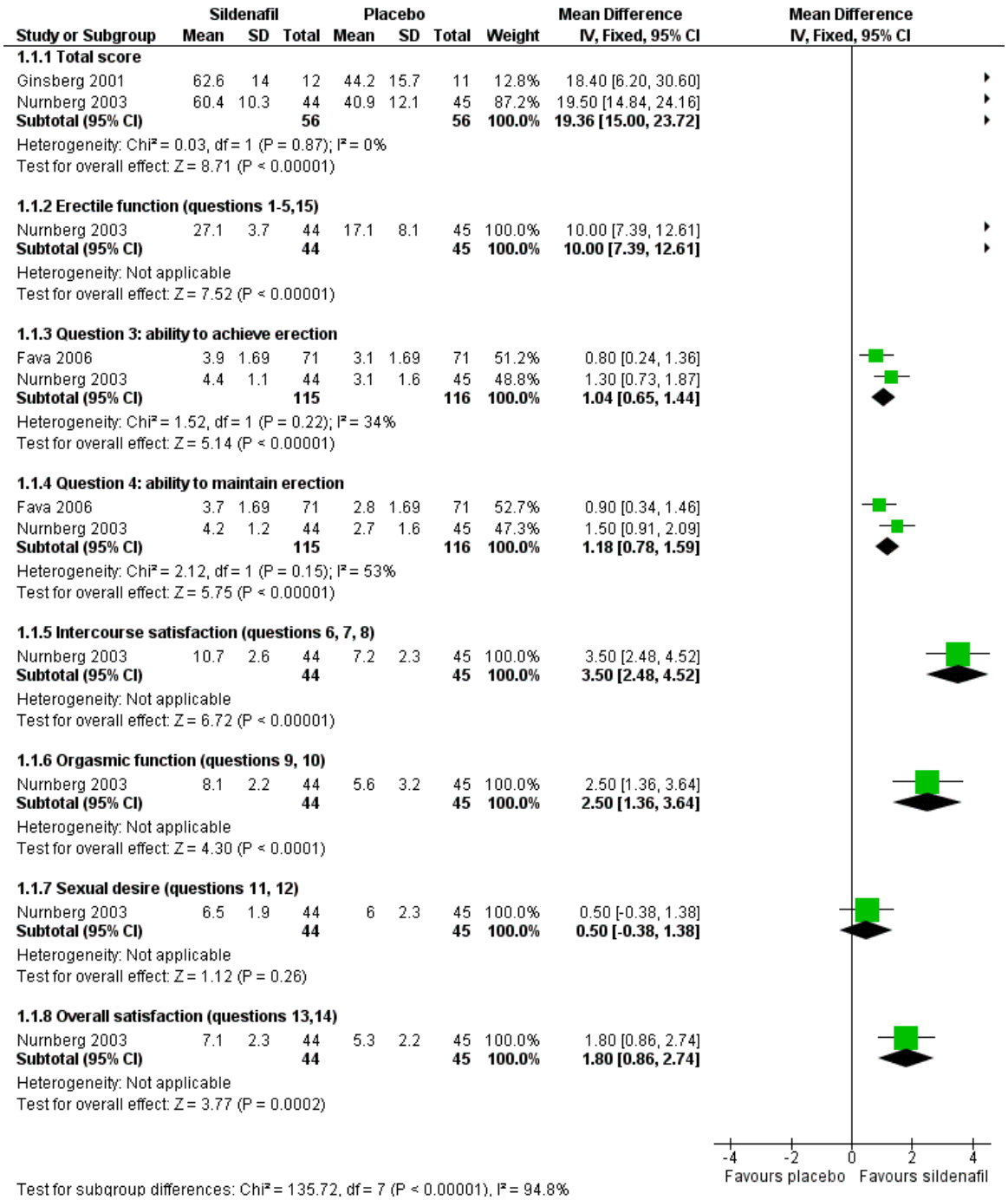
1.1 Sildenafil versus placebo

Six trials were identified that compared the effect of augmenting antidepressant treatment with sildenafil or placebo. A newer trial in men with erectile dysfunction, Fava 2006, was added to the two trials included in the original version of this review (Ginsberg 2001; Nurnberg 2003). Two trials in women were identified (Nurnberg 2002; Nurnberg 2008), but outcome data were only available from one (Nurnberg 2008). A 'Summary of findings' table is available (Summary of findings for the main comparison).

1.1.1 Effect on severity of the identified sexual dysfunction

For men, ratings of erectile dysfunction showed a benefit of sildenafil over placebo (Figure 4). Data from two studies found those receiving sildenafil scored better than those receiving placebo on questions from the IIEF regarding ability to achieve erection (MD 1.04, 95% CI 0.65 to 1.44; I^2 = 34%) and maintain erection (MD 1.18, 95% CI 0.78 to 1.59; I^2 = 53%) (Analysis 1.1) (Fava 2006; Nurnberg 2003). The remaining study in men found total ED-ITS scores also favoured sildenafil (MD 21.60, 95% CI 4.30 to 38.90) (Analysis 1.2) (Ginsberg 2001). The I^2values reported are consistent with moderate statistical heterogeneity between studies on the IIEF ratings.

Figure 4. Forest plot of comparison 1: sildenafil vs placebo, outcome: 1.1 endpoint International Index of Erectile Function (IIEF) scores

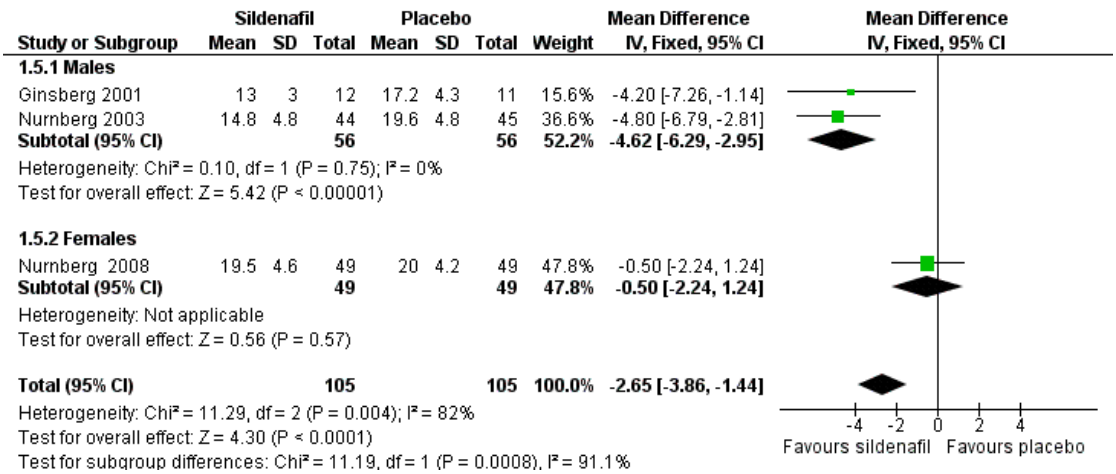


For women, ratings of overall sexual dysfunction with the clinician-rated CGI-SF favoured sildenafil (MD -0.80, 95% CI -1.20 to -0.40) (Analysis 1.3), but results with the participant-rated ASEX were consistent with benefits from either sildenafil or placebo (MD -0.50, 95% CI -2.24 to 1.24) (Analysis 1.5).

1.1.2 Effect on sexual satisfaction and functioning

Similar effects of sildenafil were observed for men (Nurnberg 2003), and women (Nurnberg 2008), on the CGI-SF (RR 0.44, 95% CI 0.33 to 0.58) (Analysis 1.4). ASEX scores from two studies in men favoured sildenafil (MD -4.62, 95% CI -6.29 to -2.95; Figure 5) (Analysis 1.5) (Ginsberg 2001; Nurnberg 2003). This appears to differ from the uncertain effect found for women as noted above. In the study in women from which data are available (Nurnberg 2008), no difference was observed between sildenafil and placebo in endpoint total scores and subscales of SFQ (Analysis 1.14), and UNM-SFI (Analysis 1.15).

Figure 5. Forest plot of comparison 1: sildenafil vs placebo, outcome: 1.5 endpoint Arizona Sexual Experience Scale (ASEX) total scores



In one study sildenafil was associated with improved scores on the MGH-SFQ for total score and all domains (Analysis 1.7) (Nurnberg 2003). The IIEF, total score, and several subdomains showed benefit from sildenafil (Analysis 1.1), although increased sexual desire was not demonstrated (MD 0.50, 95% CI -0.38 to 1.38). In another study (Fava 2006), GEQ responses indicated improvement in erections and ability to have satisfactory sexual intercourse (Analysis 1.12; Analysis 1.13).

1.1.3 Dropout rates

Reported dropout rates were consistent with effects favouring either sildenafil or placebo (RR 0.68, 95% CI 0.41 to 1.14) (Analysis 1.9).

1.1.4 Change in the primary psychiatric condition

From the two trials that provided data, endpoint HAM-D scores tended to favour sildenafil but could not exclude a benefit of placebo (MD -0.94, 95% CI -1.94 to 0.07) (Analysis 1.10); a similar pattern was seen when analysed dichotomously for loss

of remission from depression (RR 0.33, 95% CI 0.04 to 3.09) (Analysis 1.11).

1.2 Tadalafil versus placebo

One study was identified that compared the effect of treatment with tadalafil or placebo alongside antidepressant medication (Evliyaoğ lu 2011).

1.2.1 Effect on severity of the identified sexual dysfunction

Those receiving tadalafil were more likely than those on placebo to report improved erectile function on the GAQ (RR 11.50, 95% CI 3.03 to 43.67) (Analysis 2.1). IIEF data from Evliyaoğ lu 2011 are not currently available in a suitable form for meta-analysis, but qualitatively they suggest an effect on this measure for tadalafil compared to placebo.

1.2.2 Effect on sexual satisfaction and functioning

Results from use of the Sexual Encounter Profile (SEP) diary mean that a benefit of placebo could not be excluded (Analysis 2.2), including rates of overall satisfaction (RR 6.00, 95% CI 0.78 to 46.29).

1.2.3 Dropout rates

Overall rates of early discontinuation were consistent with benefits for tadalafil or placebo (RR 0.36, 95% CI 0.04 to 3.24) (Analysis 2.3), as were rates of discontinuation for apparent lack of efficacy (RR 0.36, 95% CI 0.04 to 3.24). No dropouts were attributed to adverse effects in either group.

1.2.4 Change in the primary psychiatric condition

No data were available on changes in the primary psychiatric condition.

Comparison two: Addition of bupropion

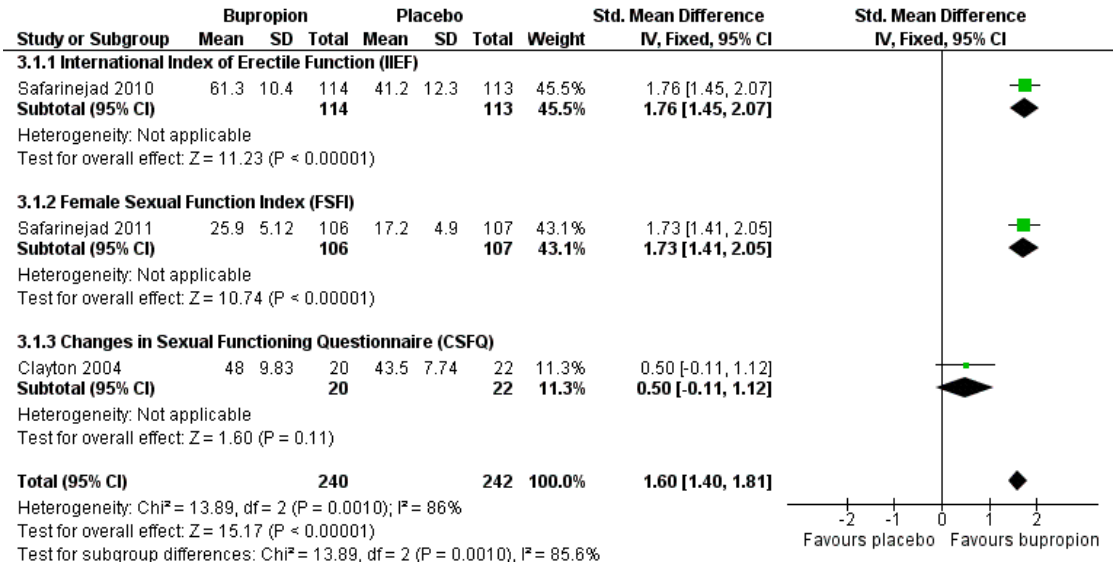
2.1 Bupropion versus placebo

There are now data available from five trials, with 579 participants, comparing the effect of augmenting antidepressant treatment with bupropion or placebo (Clayton 2004; DeBattista 2005; Masand 2001; Safarinejad 2010; Safarinejad 2011). A 'Summary of findings' table is available (Summary of findings 2).

2.1.1 Effect on severity of the identified sexual dysfunction

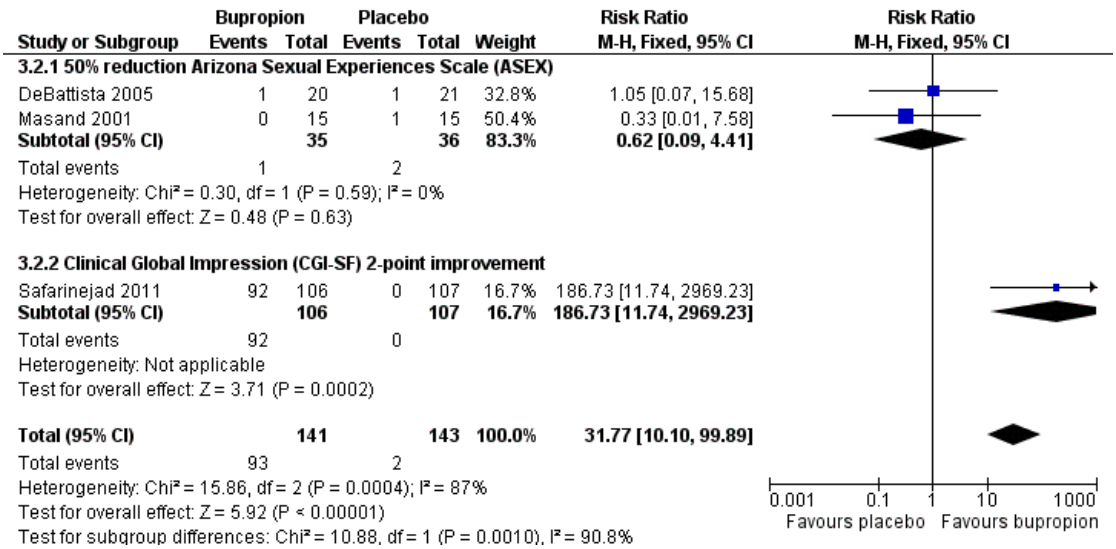
Endpoint data for the total scores on rating scales used to identify sexual dysfunction were available from three studies (Clayton 2004; Safarinejad 2010; Safarinejad 2011), which gave a standardised mean difference (SMD) of 1.60 (95% CI 1.40 to 1.81) favouring bupropion over placebo (Figure 6) (Analysis 3.1). There was a high level of statistical inconsistency identified in this analysis (I^2 = 86%), which appears to be driven by the contrast between the striking effect sizes reported in two studies (SMD 1.76, 95% CI 1.45 to 2.07; Safarinejad 2010: and SMD 1.73, 95% CI 1.41 to 2.05; Safarinejad 2011), and a more modest trend in the third (SMD 0.50, 95% CI -0.11 to 1.12; Clayton 2004). The reasons for this inconsistency are unclear.

Figure 6. Forest plot of comparison 3: bupropion vs placebo, outcome: 3.1 endpoint scale total scores



Response rates from two studies (DeBattista 2005; Masand 2001), defined as 50% reduction in ASEX score, were consistent with greater effects of either bupropion or placebo (RR 0.62, 95% CI 0.09 to 4.41; Figure 7) (Analysis 3.2), while one study found that women taking bupropion were more likely to achieve a two-point reduction on CGI-SF scores than those taking placebo (RR 186.73, 95% CI 11.74 to 2969.23) (Analysis 3.2) (Safarinejad 2011).

Figure 7. Forest plot of comparison 3: bupropion vs placebo, outcome: 3.2 response (as defined by study)



2.1.2 Effect on sexual satisfaction and functioning

Endpoint CGI-SF scores from two studies favoured bupropion (MD -1.74, 95% CI -1.87 to -1.61) (Analysis 3.8) (Safarinejad 2010; Safarinejad 2011). For men taking part in Safarinejad 2010, total scores and all subscales from IIEF, ASEX, and EDITS scales favoured bupropion over placebo (IIEF Analysis 3.3; ASEX Analysis 3.9; EDITS Analysis 3.10; Analysis 3.11). For women taking part in Safarinejad 2011, FSFI total score and subscales other than pain favoured bupropion (Analysis 3.4).
In Clayton 2004 CSFQ total scores were consistent with a greater effect of either bupropion or placebo (MD 4.50, 95% CI -0.89 to 9.89) (Analysis 3.5), as were subscales other than desire/frequency, where a benefit of bupropion was observed (MD 0.88, 95% CI 0.21 to 1.55).

2.1.3 Dropout rates

There was no statistically significant difference in dropout rates between bupropion and placebo (RR 1.08, 95% CI 0.67 to 1.72) (Analysis 3.6).

2.1.4 Change in the primary psychiatric condition

One trial reported endpoint HAM-D scores (Clayton 2004), and found no significant difference between the groups (MD -0.60, 95% CI -2.62 to 1.42) (Analysis 3.7).

Comparison three: Change of antidepressant

3.1 Nefazodone versus sertraline

One trial compared the effect of changing antidepressant to nefazodone with effect of restarting sertraline after a two-week washout period in which sertraline-induced sexual dysfunction had resolved (Ferguson 2001).

3.1.2 Effect on severity of the identified sexual dysfunction

On a physician-rated measure (PRSDS), sexual dysfunction was significantly less likely to re-emerge on treatment with nefazodone compared with restarting sertraline (RR 0.34, 95% CI 0.19 to 0.60) (Analysis 4.1). This means the number needed to treat for an additional beneficial outcome (NNTB) with nefazodone, that is for one additional person to avoid re-emergence of sexual dysfunction, was two (95% CI 2 to 4). This benefit of using nefazodone was seen by the end of the first week of treatment (Analysis 4.1).

3.1.2 Effect on sexual satisfaction and functioning

Differences in participant-rated overall sexual satisfaction did not achieve statistical significance (MD 17.22, 95% CI -4.57 to 39.01) (Analysis 4.2).

3.1.3 Dropout rates

No significant difference was noted between groups in overall dropout rates, RR 0.83 (95% CI 0.43 to 1.60) nor in dropouts attributed to adverse effects, RR 0.46 (95% CI 0.17 to 1.25).

3.1.4 Change in the primary psychiatric condition

There was no significant difference in HAM-D between the two groups at the end of the trial (MD -1.57, 95% CI -4.51 to 1.37).

Comparison four: Addition of Ginkgo biloba

4.1 *Ginkgo biloba* versus placebo

Two studies compared the effect of augmenting antidepressant treatment with *Ginkgo biloba* or placebo (Kang 2002; Wheatley 2004).

4.1.1 Effect on severity of the identified sexual dysfunction

There was no significant difference in endpoint sexual dysfunction between the groups on most questions of a nine-item questionnaire in one study (Kang 2002) . On the 'satisfaction to orgasm' question, scores were better in the placebo arm (MD -1.12, 95% CI -2.00 to -0.24). Only data from the five items assessed in both genders was provided in sufficient detail for analysis.
In the second study (Wheatley 2004), total scores on an investigator-developed scale of sexual dysfunction were compatible with a benefit of either placebo or *Ginkgo biloba* (MD 3.80, 95% CI -1.94 to 9.54) (Analysis 5.2).

4.1.2 Effect on sexual satisfaction and functioning

No other data on sexual satisfaction or functioning were reported.

4.1.3 Dropout rates

There was no significant difference in the rate of dropouts between the two arms of Kang 2002 (RR 1.33, 95% CI 0.51 to 3.43) (Analysis 5.3). There was an overall dropout rate of 22% in Wheatley 2004, but the distribution of dropouts between treatment arms was unclear.

4.1.4 Change in the primary psychiatric condition

No data were available on changes in the primary psychiatric condition from Kang 2002. Ratings of depression and anxiety symptoms were obtained by Wheatley 2004, but sufficient details are not available for analysis here.

Comparison five: Addition of granisetron

5.1 Granisetron versus placebo

Two trials compared augmentation of antidepressant treatment with granisetron to the addition of placebo (Jespersen 2004;

Nelson 2001). Data from Nelson 2001 were derived from both cross-over periods of the trial.

5.1.1 Effect on severity of the identified sexual dysfunction

In the Nelson 2001 trial both groups had similar change from baseline on SSES scores (MD 0.10, 95% CI -2.22 to 2.42). In the Jespersen 2004 trial, total scores on both ASEX and FSFSQ were consistent with greater benefit from either granisetron or placebo (ASEX MD 7.90, 95% CI -1.87 to 17.67: FSFSQ MD 1.60, 95% CI -5.46 to 8.66).

5.1.2 Effect on sexual satisfaction and functioning

In Jespersen 2004, most item scores on both ASEX and FSFSQ were consistent with greater benefit from either granisetron or placebo (Analysis 6.2; Analysis 6.3). Where items did favour one agent, placebo performed better than granisetron (FSFSQ items 1 and 2; and ASEX orgasm satisfaction).

5.1.3 Dropout rates

There was no statistically significant difference in dropout rates between the two groups in the Jespersen 2004 trial (RR 6.67, 95% CI 0.39 to 114.78) (Analysis 6.4). There was an overall dropout rate of 35% in Nelson 2001, but the distribution of the dropouts between treatments was not clear.

5.1.4 Change in the primary psychiatric condition

Rates of recurrence of mood symptoms were consistent with benefit of either agent in the Nelson 2001 study (RR 2.87, 95%CI 0.12 to 66.75) (Analysis 6.5). In the Jespersen 2004 study it was reported that CGI for depressive symptoms did not differ between groups, but insufficient details were available for analysis.

Comparison six: Addition of a 5HT1A receptor agonist

6.1 VML-670 versus placebo

Only the Baldwin 2008 study compared augmentation of antidepressant treatment with VML-670 to the addition of placebo.

6.1.1 Effect on severity of the identified sexual dysfunction

By the end of the trial, rates of absence of sexual dysfunction, defined by ASEX, were consistent with benefits of either VML-607 or placebo (RR 1.24, 95% CI 0.86 to 1.77) (Analysis 7.1), as were rates of improvement defined by CGI (RR 1.24, 95% CI 0.71 to 2.17) (Analysis 7.2).

6.1.2 Effect on sexual satisfaction and functioning

ASEX total scores were not presented with sufficient detail for analysis in this review. Items of the ASEX were mostly consistent with benefits of either VML-607 or placebo (Analysis 7.3), with the exception that men randomised to VML-670 reported a greater improvement in erectile function (MD -0.40, 95% CI -0.80 to 0.00).

6.1.3 Dropout rates

No significant difference was noted between groups in overall dropout rates (RR 0.97, 95% CI 0.56 to 1.68), or in dropouts attributed to adverse effects (RR 2.32, 95% CI 0.75 to 7.21) (Analysis 7.4).

6.1.4 Change in the primary psychiatric condition

Insufficient details on HAM-D scores were available for analysis in this review.

6.2 Buspirone versus placebo

One trial compared the effect in women of augmenting antidepressant treatment with buspirone or placebo (Michelson 2000).

6.2.1 Effect on severity of the identified sexual dysfunction

Sexual dysfunction was identified for study inclusion by clinician-rated global impression, but insufficient details of the results were presented to allow for analysis in this review.

6.2.2 Effect on sexual satisfaction and functioning

Changes in ratings on visual analogue scales of aspects of sexual functioning were consistent with benefits for either buspirone or placebo (Analysis 8.1), as was change in a summary measure of overall functioning (MD 3.10, 95% CI -38.33 to 44.53).

6.2.3 Dropout rates

No significant difference was noted between groups in overall dropout rates (RR 2.00, 95% CI 0.20 to 20.41) (Analysis 8.2)

6.2.4 Change in the primary psychiatric condition

Visual analogue scale ratings of mood (MD 0.80, 95% CI -7.61 to 9.21) and energy (MD 5.30, 95% CI -3.88 to 14.48) (Analysis 8.1) were consistent with benefits for either buspirone or placebo. Insufficient details on specific depression and anxiety rating scale scores were presented to permit analysis in this review.

Comparison seven: Addition of bethanecol

7.1 Bethanecol versus placebo

One study compared augmentation of antidepressant treatment with bethanecol against augmentation with placebo (Bernik 2004).

7.1.1 Effect on severity of the identified sexual dysfunction

Those receiving bethanecol reported higher scores than those receiving placebo on a six-point visual analogue scale of orgasmic function (MD 3.40, 95% CI 0.99 to 5.81) (Analysis 9.1).

7.1.2 Effect on sexual satisfaction and functioning

Data on erectile function were obtained, but not reported.

7.1.3 Dropout rates

Two of the 12 participants dropped out during the study, but it was unclear from which treatment group(s).

7.1.4 Change in the primary psychiatric condition

One participant (1/12) developed a depressive episode during the study, but it was unclear which treatment s/he was receiving at the time.

Comparison eight: Addition of a 5HT2 receptor antagonist

One trial compared augmentation of antidepressant treatment in women with agents including placebo and two 5HT2 receptor antagonists, olanzapine and mirtazapine (Michelson 2002). These comparisons against placebo are considered separately below:

8.1 Olanzapine versus placebo

8.1.1 Effect on severity of the identified sexual dysfunction

The group receiving olanzapine reported a greater improvement on a scale of overall sexual satisfaction completed at interview (MD -0.70, 95% CI -1.17 to -0.23). Other measures of sexual function completed at the same time were consistent with benefits for either olanzapine or placebo (Analysis 10.1).

8.1.2 Effect on sexual satisfaction and functioning

Diary ratings were all consistent with benefits for either olanzapine or placebo (Analysis 10.2).

8.1.3 Dropout rates

There was an overall dropout rate of 27%, but the distribution of dropouts between treatment group(s) was unclear. Dropouts attributed to adverse effects were consistent with benefits for either olanzapine or placebo (RR 3.59, 95% CI 0.80 to 16.21) (Analysis 10.3).

8.1.4. Change in the primary psychiatric condition

Change in mood did not differ between groups on diary ratings (MD 0.10, 95% CI -0.41 to 0.61) (Analysis 10.2). HAM-D scores were collected, but insufficient details were provided to allow for analysis.

8.2 Mirtazapine versus placebo

8.2.1 Effect on severity of the identified sexual dysfunction

Participant ratings of sexual function completed at interview were consistent with benefits for either mirtazapine or placebo (Analysis 11.1), including overall sexual satisfaction (MD 0.10, 95% CI -0.29 to 0.49).

8.2.2 Effect on sexual satisfaction and functioning

Diary ratings of overall sexual function were consistent with benefits for either mirtazapine or placebo (MD -1.30, -5.71 to 3.11), as were other diary ratings of sexual function (Analysis 11.2). Kinsey Structured Interview ratings of sexual satisfaction were better in those receiving placebo than mirtazapine (MD 0.60, 95% CI 0.19 to 1.01) (Analysis 11.3).

8.2.3 Dropout rates

There was an overall dropout rate of 27%, but the distribution of the dropouts between treatments was unclear. More participants dropped out of the mirtazapine group than the placebo group because of adverse effects (RR 6.50, 95% CI 1.56 to 27.07) (Analysis 11.4).

8.2.4 Change in the primary psychiatric condition

Change in mood did not differ between groups on diary ratings (MD -0.40, 95% CI -0.93 to 0.13). Changes in ratings of energy were better in those receiving mirtazapine (MD -0.70, 95% CI -1.38 to -0.02) (Analysis 11.2). HAM-D scores were collected, but insufficient details were provided to allow for analysis.

Comparison nine: Yohimbine versus placebo

One trial compared augmentation of antidepressant treatment in women with yohimbine or placebo (Michelson 2002), and provided outcome data for this review. A second study has also been performed (Jacobsen 1996), but data were not available in a form suitable for analysis in this review.

9.1. Effect on severity of the identified sexual dysfunction

Participant ratings of sexual function completed at interview were consistent with benefits for either yohimbine or placebo (Analysis 12.1), including overall sexual satisfaction (MD -0.30, 95% CI -0.79 to 0.19).

9.2. Effect on sexual satisfaction and functioning

Diary ratings of overall sexual function were consistent with benefits for either yohimbine or placebo (MD 1.20, 95% CI -3.24 to 5.64), as were other diary ratings of sexual function (Analysis 12.2).

9.3. Dropout rates

There was an overall dropout rate of 27%, but the distribution of dropouts between treatment group(s) was unclear. Dropouts

attributed to adverse effects were consistent with benefits for either yohimbine or placebo (RR 2.23, 95% CI 0.43 to 11.43) (Analysis 12.3).

9.4. Change in the primary psychiatric condition

Change in mood did not differ between groups on diary ratings (MD 0.10, 95% CI -0.41 to 0.61) (Analysis 12.2). HAM-D scores were collected, but insufficient details were provided to allow for analysis.

Comparison ten: Amantadine versus placebo

One trial compared augmentation of antidepressant treatment in women with amantadine or placebo (Michelson 2000).

10.1. Effect on severity of the identified sexual dysfunction

Sexual dysfunction was identified for study inclusion by clinician-rated global impression, but insufficient details of the results were presented to allow for analysis here.

10.2. Effect on sexual satisfaction and functioning

Changes in ratings on visual analogue scales of aspects of sexual functioning were consistent with benefits for either amantadine and placebo (Analysis 13.1).

10.3. Dropout rates

No significant difference was noted between groups in overall dropout rates (RR 1.11, 95% CI 0.07 to 16.47) (Analysis 13.2).

10.4. Change in the primary psychiatric condition

Participants randomised to amantadine reported a greater increase in ratings of both mood (MD 8.10, 95% CI 1.23 to 14.97) and energy (MD 12.70, 95% CI 5.30 to 20.10) (Analysis 13.1). Insufficient details on specific depression and anxiety rating scale scores were presented to allow for analysis here.

Comparison eleven: Ephedrine versus placebo

One trial compared the effect of augmenting antidepressant treatment with ephedrine or placebo (Meston 2004). Data were derived from both cross-over periods of the trial.

11.1. Effect on severity of the identified sexual dysfunction

Ratings at the end of treatment on the BISF-W were consistent with benefits from either ephedrine or placebo (Analysis 14.1).

11.2. Effect on sexual satisfaction and functioning

No measures to assess sexual satisfaction and functioning were employed in this trial.

11.3. Dropout rates

There was an overall dropout rate of 34%, but the distribution of dropouts between treatment group(s) was unclear.

11.4. Change in the primary psychiatric condition

Ratings of depression were made, but insufficient details were presented to allow for analysis here.

Comparison twelve: Maca root low dose (1.5 g) versus maca root high dose (3 g)

One study was identified that assessed the effects of two different doses of maca root on antidepressant-induced sexual dysfunction (Dording 2008).

12.1. Effect on severity of the identified sexual dysfunction

Participants randomised to either dose of maca root reported similar endpoint ratings by ASEX total score (MD -0.80, 95% CI -6.49 to 4.89) (Analysis 15.1) and MGH-SFQ total score (MD -2.00, 95% CI -7.69 to 3.69) (Analysis 15.2).

12.2. Effect on sexual satisfaction and functioning

Similarly, ratings of sexual desire items from both ASEX (MD 0.30, 95% CI -1.38 to 1.98) (Analysis 15.1) and MGH-SFQ (MD -0.10, 95% CI -1.62 to 1.42) (Analysis 15.2) were similar between groups.

12.3. Dropout rates

Rates of overall dropout did not differ between groups (RR 1.50, 95% CI 0.60 to 3.74) (Analysis 15.3).

12.4. Change in the primary psychiatric condition

The HAM-D total endpoint score was not significantly different between the groups (MD -2.50, 95% CI -7.98 to 2.98) nor was the HAM-A total endpoint score (MD -0.40, 95% CI -3.15 to 2.35) (Analysis 15.4).

Subgroup and sensitivity analyses

Due to the small number of studies in each comparison we were unable to conduct the planned subgroup and sensitivity analyses.

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Bupropion compared with placebo for antidepressant-induced sexual dysfunction

Patient or population: people with antidepressant-induced sexual dysfunction
Settings: outpatients
Intervention: bupropion (doses of 150 mg daily and 150 mg twice daily)
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (no of studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Bupropion				
Endpoint scale total scores (150 mg twice daily dose) (Scales of sexual functioning. As studies used different scales to assess sexual functioning, differences are expressed as standardised mean differences (SMD))	The mean value with this analysis is in effect zero	The mean score in the intervention groups was 1.60 higher (1.40 to 1.81)		482 (3 studies)	⊕⊕⊕◯ **moderate**[1]	
50% reduction in score on the Arizona Sexual Experiences Scale (ASEX) (150 mg once daily dose) (The ASEX is a 5-item self-report inventory of sexual function)	**Lower risk population**		**RR** 0.62 (0.09 to 4.41)	71 (2 studies)	⊕⊕⊕◯ **moderate**	
	47 per 1000	**29 per 1000** (4 to 208)				
	Higher risk population					
	67 per 1000	**41 per 1000** (6 to 296)				

Dropouts (People leaving the trial early)	**Lower risk population**		**RR** 1.08 (0.67 to 1.72)	579 (5 studies)	⊕⊕⊕⊕ **high**
	90 per 1000	**97 per 1000** (60 to 155)			
	Higher risk population				
	150 per 1000	**162 per 1000** (100 to 258)			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk Ratio

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

[1] Unexplained inconsistency in effects between studies reduces confidence in this effect

DISCUSSION

Summary of main results

Twenty-three trials involving 1886 people met the inclusion criteria for the updated review. The original version of this review included 15 studies with around 900 participants randomised, so there has been a substantial increase in the data available from randomised trials to address this area of interest. This update has included both increased data for previously identified strategies (addition of sildenafil or bupropion) and trials of new agents for this indication. All except one trial (Ferguson 2001) assessed the addition of further medication to treat the sexual dysfunction.

We were unable to do the intended subgroup analyses by gender, but these are summarised descriptively here to facilitate interpretation.

Men

In men, data for the phosphodiesterase inhibitors sildenafil (three studies, 255 participants; see Summary of findings for the main comparison) and tadalafil (one study, 54 participants) indicated that they led to a greater improvement in erectile function than placebo. The estimates of treatment effect observed are similar to those reported for their use in erectile dysfunction due to other causes (Fink 2002; Carson 2004).

In men, addition of higher dose bupropion has also shown benefit (see Summary of findings 2), but this is primarily shown in a single study (234 participants; Safarinejad 2010). Replication of this effect is likely to increase confidence in this finding. The magnitude of effect seen on total IIEF score (MD 20.10, 95% CI 17.14 to 23.06) (Analysis 3.3) was similar to that seen in studies of sildenafil (MD 19.36, 95% CI 15.00 to 23.72) (Analysis 1.1). There are also some promising data from a small cross-over trial of bethanecol suggesting benefit for men with antidepressant-induced ejaculatory delay or anorgasmia rather than erectile dysfunction (Bernik 2004). Replication in further studies is likely to be necessary for clinicians and patients to have confidence in this effect.

Women

For women it remains uncertain whether sildenafil is more effective than placebo, but outcome data are only available from one study (Nurnberg 2008). We have identified a larger unpublished study (Nurnberg 2002) - if results from this second study were to become available, it would be expected to reduce this uncertainty substantially.

Data from studies of bupropion 150 mg twice daily indicate a benefit over placebo. These included a study that predominantly included women (Clayton 2004), and one solely in women (Safarinejad 2011). However, response rates in two studies of bupropion 150 mg once daily were consistent with superiority of either bupropion or placebo. The two-point improvement in CGI taken as a measure of response in Safarinejad 2011 is equivalent to an improvement in rating from 'markedly' to 'mildly' impaired function, which may be a clinically significant change.

Both sexes

Other augmentation strategies studied failed to show significant improvements in sexual dysfunction compared with placebo

One trial involving 75 participants of both genders with sexual dysfunction due to sertraline assessed the effect of changing the antidepressant. Switching to nefazodone was significantly less likely to result in the re-emergence of sexual dysfunction than restarting sertraline, and was not associated with any worsening of depression. However, since nefazodone is no longer available for use, this strategy is now of limited usefulness.

Adverse effects

We hypothesised that management strategies for antidepressant-induced sexual dysfunction might differ in acceptability or be associated with a worsening of the condition for which antidepressants were originally being taken. We have identified no data for any of the strategies assessed here that indicated they led to a worsening of psychiatric symptoms. However, the relatively small numbers assessed for many of the interventions studied means that the possibility of such an effect cannot confidently be excluded in all cases.

Rates of dropout from studies with different treatments were not clearly presented in all cases. From the available data, only one intervention was associated with an increase in people dropping out of the study, which was augmentation with mirtazapine (Michelson 2002). However, the analysis of this four-arm study does not correct for the multiple statistical comparisons that result, and therefore the 95% confidence intervals presented may overestimate the confidence with which this effect has been shown. Further randomised trial data may act to reduce this uncertainty.

Overall completeness and applicability of evidence

The available data mostly investigate the strategy of adding additional medication to counteract antidepressant-induced sexual dysfunction. There is an absence of randomised data that assesses switching to currently-available antidepressant agents with lower rates of sexual adverse effects, the role of psychological or mechanical interventions (Hawton 1995), or of techniques such as drug holidays. There is a particular need for more evidence to guide treatment of antidepressant-induced sexual dysfunction in women. The ongoing studies identified suggest that this limitation of the evidence-base will be only partially be addressed in the foreseeable future. Of the six studies identified, only one is investigating change of antidepressant (Takeda 2011), and only one other

is investigating *Ginkgo biloba*, sex therapy, and a combination of the two (Meston 2008).

Quality of the evidence

Twenty-three trials involving 1886 people were included in this review. Many studies were unclear in their reporting of methods, which leaves uncertainty regarding the extent to which their results are subject to bias (see Figure 2). Use of a double-blind design was commonly reported, but there was generally little information provided on methods used for randomisation or to maintain concealment of allocation. Studies may have been vulnerable to reporting bias, since original study protocols were not available, and, in some cases, only data from particular subscales or questions within a larger scale were reported.

There is now a strong and internally consistent evidence base for the use of phosphodiesterase inhibitors for antidepressant-induced erectile dysfunction in men. For women with antidepressant-induced sexual dysfunction, the addition of bupropion at higher doses appears to be the most promising approach studied so far, however, unexplained inconsistencies in effects between studies remain, reducing the confidence with which this strategy can be advocated.

Potential biases in the review process

While we have made efforts to be comprehensive in our methods to identify all published studies, given the small numbers of studies that investigated most of the strategies assessed, the presence of any unpublished trials could have substantial effects on estimates of effect. In some cases, only results from particular items or subscales within ratings scales are available. It is likely that this could act to bias estimates of effect obtained, increasing apparent effectiveness. The investigation of multiple strategies and often multiple outcomes for each strategy within this review will have increased the risk of reporting false positive findings of effectiveness.

Agreements and disagreements with other studies or reviews

The Cochrane Review on the management of sexual dysfunction due to antipsychotic drug therapy similarly found some support for the addition of sildenafil in men (Schmidt 2012), but the evidence available came from only one small study (32 participants). We are not aware of any non-Cochrane systematic reviews on this topic.

AUTHORS' CONCLUSIONS

Implications for practice

The evidence currently available is rather limited. For men with antidepressant-induced erectile dysfunction, the addition of sildenafil or tadalafil appears to be an effective strategy, and there are some promising data for bupropion. For women with antidepressant-induced sexual dysfunction, the addition of bupropion at higher doses appears to be the most promising approach studied so far.

Implications for research

Further randomised trials are required. There is a particular need for more evidence to guide treatment of antidepressant-induced sexual dysfunction in women. Addition of bupropion to existing treatment warrants further study. Randomised trials could assess approaches for which there is currently an absence of evidence, including: switching to currently-available antidepressant agents with lower rates of sexual adverse effects, the role of psychological or mechanical interventions, or of techniques such as drug holidays. Outcome assessments using standardised ratings scales should be included.

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Dording 2010 *{published data only}*
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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Baldwin 2008

Methods	Double-blind, multicentreD (37 sites), parallel group, 4-week duration
Participants	288 adults (ages 22-67 years) randomised (84 men, 204 women) Inclusion criteria: sexually active at least once a week; sexual dysfunction treatment-emergent; ASEX score 19 or more; stable dosage of fluoxetine or paroxetine for at least 8 weeks prior to screening and for 3 months Exclusion criteria: HAM-D score of 12 or more
Interventions	1. VML-670 (300 μg once daily) or, 2. Placebo daily
Outcomes	Assessed with following scales: ASEX, CGI, HAM-D
Notes	37 UK primary care sites VML-670 is a 5-HT1A receptor agonist

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated schedule
Allocation concealment (selection bias)	Unclear risk	-
Blinding (performance bias and detection bias) All outcomes	Low risk	All study personnel and participants were blinded to treatment assignment for duration of the study
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All study personnel and participants were blinded to treatment assignment for duration of the study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All study personnel and participants were blinded to treatment assignment for duration of the study
Incomplete outcome data (attrition bias) All outcomes	Low risk	-
Selective reporting (reporting bias)	Unclear risk	-

Bernik 2004

Methods	Double-blind, 2 period cross-over design, 2 weeks of active treatment
Participants	12 men (aged 18-65 years) randomised Inclusion criteria: In remission from panic disorder; treated with clomipramine; ejaculatory delay or anorgasmia (no participants with erectile dysfunction)
Interventions	1. Bethanecol chloride 20 mg as needed (taken 45 minutes before sexual intercourse on up to 2 occasions in each 2-week period), or 2. Placebo
Outcomes	Changes in VAS sexual function scale
Notes	Trial performed in Brazil Bethanecol has mixed central and peripheral cholinergic and adrenergic effects

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	-
Allocation concealment (selection bias)	Unclear risk	-
Blinding (performance bias and detection bias) All outcomes	Low risk	'Double blind'
Blinding of participants and personnel (performance bias) All outcomes	Low risk	'Double blind'
Blinding of outcome assessment (detection bias) All outcomes	Low risk	'Double blind'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	-
Selective reporting (reporting bias)	Unclear risk	-

Clayton 2004

Methods	Double-blind, parallel-arm, multicentred (3 sites), 4-weeks duration
Participants	55 adults (aged 18-45 years) randomised (48 women, 7 men). Includsion criteria: DSM-IV depression with sustained remission; developed or worsened sexual problems on current SSRI treatment

Clayton 2004 (*Continued*)

Interventions	1. Bupropion SR 150 mg (once daily for 3 days, increasing to twice daily if tolerated) in addition to SSRI, or 2. Placebo twice daily, in addition to SSRI
Outcomes	CSFQ, HAM-D
Notes	USA sites Bupropion is thought to act by dual inhibition of norepinephrine and dopamine reuptake

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	-
Allocation concealment (selection bias)	Unclear risk	-
Blinding (performance bias and detection bias) All outcomes	Low risk	'Double blind'
Blinding of participants and personnel (performance bias) All outcomes	Low risk	'Double blind'
Blinding of outcome assessment (detection bias) All outcomes	Low risk	'Double blind'
Incomplete outcome data (attrition bias) All outcomes	Low risk	No incomplete data
Selective reporting (reporting bias)	Unclear risk	-

DeBattista 2005

Methods	Double-blind, parallel-arm trial, 6-week duration
Participants	41 adults (aged 18-60 years) randomised (17 men, 24 women). Inclusion criteria: stable dose of fluoxetine, paroxetine, citalopram or sertraline for at least 6 weeks; sexual side effects which participants believed were temporally related to the antidepressant use; ASEX score of at least 15
Interventions	1. Bupropion SR 150 mg once daily for six weeks, in addition to current SSRI, or 2. Placebo for six weeks, in addition to current SSRI
Outcomes	ASEX, HAM-D, Beck Depression Inventory

DeBattista 2005 (*Continued*)

Notes	Trial performed in USA Bupropion is thought to act by dual inhibition of norepinephrine and dopamine reuptake

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	-
Allocation concealment (selection bias)	Unclear risk	-
Blinding (performance bias and detection bias) All outcomes	Low risk	'Double blind'
Blinding of participants and personnel (performance bias) All outcomes	Low risk	'Double blind'
Blinding of outcome assessment (detection bias) All outcomes	Low risk	'Double blind'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	-
Selective reporting (reporting bias)	High risk	No outcome data reported for secondary measures

Dording 2008

Methods	Parallel group trial, 12 weeks of treatment
Participants	20 adults (3 men, 17 women) Inclusion criteria: depression in remission (HAM-D < 10); SSRI-induced sexual dysfunction for at least 4 weeks (no sexual dysfunction before antidepressant, clear temporal relationship between antidepressant and dysfunction)
Interventions	1. Maca root (*Lepidium meyenii*) extract 3.0 g/day, or 2. Maca root (*L meyenii)* extract 1.5 g/day
Outcomes	ASEX, MGH-SFQ, HAM-D, HAM-A
Notes	Trial performed in USA Maca, also known as "Peruvian Ginseng," is a plant traditionally used for medicinal purposes

Dording 2008 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	-
Allocation concealment (selection bias)	Unclear risk	-
Blinding (performance bias and detection bias) All outcomes	Low risk	'Double blind'
Blinding of participants and personnel (performance bias) All outcomes	Low risk	'Double blind'
Blinding of outcome assessment (detection bias) All outcomes	Low risk	'Double blind'
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Unclear risk	-

Evliyaoğlu 2011

Methods	Parallel group trial, 12-week duration
Participants	54 men (aged 23-74 years) randomised. Inclusion criteria: sexual dysfunction emerged during antidepressant (SRI) treatment; dysfunction continued for 4 weeks or more
Interventions	1. Tadalafil 20 mg, or 2. Placebo Tadalafil or placebo taken 1 h before sexual activity, and not more than once daily
Outcomes	IIEF; SEP diary; Global Assessment Questions
Notes	Trial performed in Turkey Tadalafil is a phosphodiesterase type 5 inhibitor

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Random sequence generation (selection bias)	Unclear risk	States 'randomly assigned', but no details provided on method of sequence generation
Allocation concealment (selection bias)	Unclear risk	-
Blinding (performance bias and detection bias) All outcomes	Low risk	'Participants, physicians and data collators were unaware of the treatment assignment of the patients'
Blinding of participants and personnel (performance bias) All outcomes	Low risk	'Participants, physicians and data collators were unaware of the treatment assignment of the patients'
Blinding of outcome assessment (detection bias) All outcomes	Low risk	'Participants, physicians and data collators were unaware of the treatment assignment of the patients'
Incomplete outcome data (attrition bias) All outcomes	Low risk	No incomplete data
Selective reporting (reporting bias)	Low risk	All outcomes described

Fava 2006

Methods	Double-blind, parallel-arm trial, 6-week duration
Participants	142 men (aged 27-74 years) randomised. Inclusion criteria: SSRI-associated erectile dysfunction (Sexual Health Inventory for Men score > 20); no erectile dysfunction prior to antidepressant; DSM-IV major depressive disorder currently in remission (HAM-D < 10); taking SRI for 8 weeks or more, and stable dose for 4 weeks
Interventions	1. Sildenafil 50 mg daily initially then variable dose later (25-100 mg depending on efficacy and tolerability), or 2. Placebo
Outcomes	IIEF, Erectile Dysfunction Inventory of Treatment Satifisaction, Global Efficacy Questionnaire, HAM-D, Beck Anxiety Inventory
Notes	Centres in USA, Germany, UK, Canada Sildenafil is a phosphodiesterase inhibitor

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomly assigned using a computer algorithm of random permuted blocks

Fava 2006 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	-
Blinding (performance bias and detection bias) All outcomes	Low risk	'Double blind'
Blinding of participants and personnel (performance bias) All outcomes	Low risk	'Double blind'
Blinding of outcome assessment (detection bias) All outcomes	Low risk	'Double blind'
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Unclear risk	-

Ferguson 2001

Methods	Double-blind, parallel-arm, multicentreD (9 sites) trial, 10-week duration
Participants	75 adults (aged 18-65 years) randomised (34 women, 38 men). Inclusion criteria: DSM-III-R moderate or severe depressive episode; sexual dysfunction due to sertraline; judged clinically stable and able to discontinue sertraline; all symptoms of sexual dysfunction absent during placebo run-in phase
Interventions	1-week washout period when sertraline treatment suspended, then 7-10 day placebo lead in, then: 1. Nefazodone 100 mg twice daily increasing to 200 mg after 1 week, or 2. Sertraline 50 mg once daily increasing to 100 mg after 1 week and placebo at night
Outcomes	Physician's rating of sexual dysfunction, modified version of Rush-Presbyterian Sexual Function Inventory, HAM-D, CGI (for depressive symptoms)
Notes	Trial performed in USA, 9 sites

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details of sequence generation method provided
Allocation concealment (selection bias)	Unclear risk	-

Ferguson 2001 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Low risk	'Double blind'
Blinding of participants and personnel (performance bias) All outcomes	Low risk	'Double blind'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	'Double blind'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Three of 75 participants randomised excluded from efficacy analyses
Selective reporting (reporting bias)	Unclear risk	-

Ginsberg 2001

Methods	Double-blind, parallel-arm trial, 8-week duration
Participants	23 men (aged 30-64 years). Inclusion criteria: clinically recovered mood or anxiety disorder; SSRI associated sexual dysfunction (SSRI or venlafaxine); medications stable for 4 weeks prior and during study
Interventions	1. Sildenafil 50-100 mg once daily for 8 weeks, or 2. Placebo for 8 weeks
Outcomes	IIEF, ASEX, Erectile Dysfunction Inventory of Treatment Satifsaction, Rigiscan
Notes	Multicentred Sildenafil is a phosphodiesterase inhibitor

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	-
Allocation concealment (selection bias)	Unclear risk	-
Blinding (performance bias and detection bias) All outcomes	Low risk	'Double blind'

Ginsberg 2001 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	'Double blind'
Blinding of outcome assessment (detection bias) All outcomes	Low risk	'Double blind'
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	High risk	Not all outcomes reported (abstract, not full publication)

Jacobsen 1996

Methods	Cross-over design, 2 sequential 3-week trials
Participants	33 participants (11 men, 22 women). Inclusion criteria: sexual dysfunction after starting SRI treatment; DSM-IV major depression, bipolar disorder, or obsessive compulsive disorder; fluoxetine or sertraline taken for at least 8 weeks prior to study entry
Interventions	1. Yohimbine 5.4 mg three times daily, or 2. Placebo three times daily
Outcomes	4-point scales for libido, orgasm, erection (men), mood, anxiety, sleep disturbance, gastrointestinal distress, flushing
Notes	Trial performed in USA Yohimbine blocks alpha-2 adrenoceptors

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	-
Allocation concealment (selection bias)	Unclear risk	-
Blinding (performance bias and detection bias) All outcomes	Low risk	'Double blind'
Blinding of participants and personnel (performance bias) All outcomes	Low risk	'Double blind'

Jacobsen 1996 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	'Double blind'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear whether more than 33 people randomised
Selective reporting (reporting bias)	Unclear risk	-

Jespersen 2004

Methods	Double-blind, parallel-arm trial, 14-day duration
Participants	12 women (age range unclear) randomised. Inclusion criteria: antidepressant-induced sexual dysfunction; past diagnosis of depression (by MINI neuropsychiatric interview); no change in psychotropic treatment in previous 2 months; no comorbid psychiatric or medical disorder; no past history of sexual dysfunction
Interventions	1. Granisetron (dose not specified), or 2. Placebo
Outcomes	FSFSQ, ASEX, CGI ratings of depressive symptoms
Notes	Trial performed in South Africa. Granisetron is a 5-HT3 antagonist

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details of random sequence generation provided
Allocation concealment (selection bias)	Unclear risk	-
Blinding (performance bias and detection bias) All outcomes	Low risk	'Double blind'
Blinding of participants and personnel (performance bias) All outcomes	Low risk	'Double blind'
Blinding of outcome assessment (detection bias) All outcomes	Low risk	'Double blind'

Jespersen 2004 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Unclear risk	-

Kang 2002

Methods	Double-blind, parallel-arm, single-centre trial, 2-month duration
Participants	37 adults randomised (27 men, 10 women). Inclusion criteria: DSM-IV substance-induced sexual dysfunction; antidepressant treatment of depressive disorder (without psychotic features) or anxiety disorder; regular sexual activity
Interventions	1. *Ginkgo biloba* (EGb761) 120 mg/day increasing to 160 mg/ day after 2 weeks, and increasing to 240 mg/day after 4 weeks, or 2. Placebo
Outcomes	Investigator-developed questionnaire, Beck Depression Inventory (Korean version), State-Trait Anxiety Inventory
Notes	Trial performed in South Korea

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	'Random number table'
Allocation concealment (selection bias)	Unclear risk	-
Blinding (performance bias and detection bias) All outcomes	Low risk	'Double blind'
Blinding of participants and personnel (performance bias) All outcomes	Low risk	'Double blind'
Blinding of outcome assessment (detection bias) All outcomes	Low risk	'Double blind'
Incomplete outcome data (attrition bias) All outcomes	Low risk	

Kang 2002 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	-

Masand 2001

Methods	Double-blind, parallel-arm trial, 3-week duration
Participants	31 adults randomised (breakdown by gender unknown). Inclusion criteria: receiving SSRI for at least 6 weeks; sexual dysfunction attributed to SSRI (ASEX score: total score of 19 or more on the ASEX scale or any individual item score > 5 or any 3 items equal to 4); HAM-D score < 10
Interventions	1. Bupropion SR 150 mg daily, or 2. Placebo
Outcomes	ASEX, HAM-D, UKU side effects rating scale
Notes	Trial performed in the USA

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	-
Allocation concealment (selection bias)	Unclear risk	-
Blinding (performance bias and detection bias) All outcomes	Low risk	'Double blind'
Blinding of participants and personnel (performance bias) All outcomes	Low risk	'Double blind'
Blinding of outcome assessment (detection bias) All outcomes	Low risk	'Double blind'
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Unclear risk	-

Meston 2004

Methods	Double-blind, cross-over design, 8-week duration
Participants	29 women randomised. Inclusion criteria: SSRI for depression; at least 10 weeks treatment; treatment otherwise successful; sexual dysfunction onset not less than 1 week and not more than 3 months after beginning SSRI; sexual dysfunction distinctly different from any noticed during depressed phase
Interventions	1. Ephedrine 50 mg once daily, or 2. Placebo Treatments to be taken approximately 1 h before sexual activity
Outcomes	BISF-W, Beck Depression Inventory
Notes	Trial performed in USA

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information on sequence generation method provided
Allocation concealment (selection bias)	Unclear risk	-
Blinding (performance bias and detection bias) All outcomes	Low risk	'Double blind'
Blinding of participants and personnel (performance bias) All outcomes	Low risk	'Double blind'
Blinding of outcome assessment (detection bias) All outcomes	Low risk	'Double blind'
Incomplete outcome data (attrition bias) All outcomes	Low risk	-
Selective reporting (reporting bias)	Unclear risk	-

Michelson 2000

Methods	Double-blind, parallel-arm, multicentred trial (3 sites), 8 weeks of treatment
Participants	61 women (aged 50 years or younger) randomised. Inclusion criteria: stable dose of fluoxetine for at least 8 weeks; impaired orgasm or sexual arousal or vaginal lubrication with onset after initiation of fluoxetine; CGI sexual function score of at least 3, HAM-D score < 11
Interventions	1. Buspirone 10 mg twice daily increasing to 15 mg in addition to fluoxetine, or 2. Amantadine 50 mg once daily increasing to 50 mg twice daily in addition to fluoxetine, or 3. Placebo twice daily, in addition to fluoxetine
Outcomes	Interviewer Rating of Sexual Function, Participant-rated VAS for sexual function, Clinician-rated global impression and participant-rated global impression, HAM-D, Beck Depression Inventory, State-Trait Anxiety Inventory
Notes	Trial performed in USA. Buspirone is a 5HT-1A agonist Amantadine is thought to increase dopamine availability

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details of sequence generation method provided
Allocation concealment (selection bias)	Unclear risk	-
Blinding (performance bias and detection bias) All outcomes	Low risk	'Patients and efficacy raters were blinded to treatment assignment and to the criteria for study entry and dose adjustments'
Blinding of participants and personnel (performance bias) All outcomes	Low risk	'Patients and efficacy raters were blinded to treatment assignment and to the criteria for study entry and dose adjustments'
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Patients and efficacy raters were blinded to treatment assignment and to the criteria for study entry and dose adjustments
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Data analysed from 57 out of total of 61 randomised
Selective reporting (reporting bias)	Unclear risk	-

Michelson 2002

Methods	Double-blind, parallel-arm. multicentred trial (12 centres), 6-week treatment period
Participants	148 women randomised. Inclusion criteria: stable dose of fluoxetine leading to reduced lubrication, or orgasmic dysfunction, or both; condition for which fluoxetine prescribed responded satisfactorily
Interventions	1. Mirtazapine 15 mg once daily increasing to 30 mg in addition to fluoxetine, or 2. Yohimbine 5.4 mg once daily increasing to 10.8 mg in addition to fluoxetine, or 3. Olanzapine 2.5 mg once daily increasing to 5 mg in addition to fluoxetine, or 4. Placebo, in addition to fluoxetine. Medications taken daily 1-2 h before sexual activity
Outcomes	Participant-assessment of sexual function, Daily diary VAS, Kinsey Ratings of Sexual Function - computer-assisted structured interview
Notes	Trial performed in USA. Mirtazapine is a 5HT2 and alpha-2 adrenergic antagonist. Yohimbine is an alpha-2 adrenergic antagonist. Olanzapine is a 5HT2 antagonist (and dopamine antagonist)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No data on sequence generation method provided
Allocation concealment (selection bias)	Unclear risk	-
Blinding (performance bias and detection bias) All outcomes	Low risk	'Double blind'
Blinding of participants and personnel (performance bias) All outcomes	Low risk	'Double blind'
Blinding of outcome assessment (detection bias) All outcomes	Low risk	'Double blind'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	-
Selective reporting (reporting bias)	Unclear risk	-

Nelson 2001

Methods	Double-blind, cross-over design, 6-week duration
Participants	20 adults randomised (2 men, 18 women). Inclusion criteria: sexual dysfunction began whilst taking SSRI; HAM-D score < 10
Interventions	1. Granisetron 1-2 mg, as required, in addition to SSRI, or 2. Placebo, in addition to SSRI. Medication taken 1-2 h prior to sexual activity
Outcomes	SSES, HAM-D
Notes	Trial performed in USA. Granisetron is a 5-HT3 antagonist

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details of sequence generation method provided
Allocation concealment (selection bias)	Unclear risk	-
Blinding (performance bias and detection bias) All outcomes	Low risk	'Double blind'
Blinding of participants and personnel (performance bias) All outcomes	Low risk	'Double blind'
Blinding of outcome assessment (detection bias) All outcomes	Low risk	'Double blind'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	-
Selective reporting (reporting bias)	Unclear risk	-

Nurnberg 2008

Methods	Double-blind, randomised, placebo-controlled, multicentred trial, 8-week duration
Participants	98 women randomised, aged 18-50 years. Includsion criteria: substance-induced sexual dysfunction to DSM-IV criteria; major depressive disorder, in remission; taking antidepressant with serotonin reuptake inhibition action for at least 8 weeks; persistent sexual dysfunction for at least 4 weeks

Interventions	1. Sildenafil, flexible dose between 50 mg and 100mg, or 2. Placebo Medication taken 1-2 h before sexual activity, not more than once daily
Outcomes	CGI scale, Sexual Function Questionnaire, ASEX, University of New Mexico Sexual Function Inventory - female version
Notes	Trial performed in USA - 7 centres

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Used an unrestricted computer-generated randomisation schedule using SPSS version 10, restriction to this randomisation was that the groups had to be of equal size
Allocation concealment (selection bias)	Low risk	The randomisation schedule was given to an independent pharmacy Medications were sealed in sequentially-numbered identical containers according to allocation sequence
Blinding (performance bias and detection bias) All outcomes	Low risk	All study personnel and participants were blinded to treatment assignment for the duration of the study
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All study personnel and participants were blinded to treatment assignment for the duration of the study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All study personnel and participants were blinded to treatment assignment for the duration of the study
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	-
Selective reporting (reporting bias)	Unclear risk	-

Nurnberg 2002

Methods	Multicentred, double-blind, placebo-controlled trial, 8-week duration, followed by single-blind, open-label 8-week extension
Participants	150 women. Inclusion criteria: major depressive disorder in remission; serotonergic reuptake inhibitor-associated female sexual dysfunction; no pre-existing sexual dysfunction; 38 weeks stable dose SRI; HAM-D score < 10; significant sexual dysfunction by CGI-SF
Interventions	1. Sildenafil (50-100 mg flexible dose), or 2. Matching placebo
Outcomes	CGI-SF, HAM-D
Notes	Limited information, no outcome data available from end of randomised phase Outcomes reported after further open-label sildenafil treatment

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	-
Allocation concealment (selection bias)	Unclear risk	-
Blinding (performance bias and detection bias) All outcomes	Unclear risk	-
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	-
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	-
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	-
Selective reporting (reporting bias)	Unclear risk	-

Nurnberg 2003

Methods	Multicentred (3 centres), double-blind, parallel-arm trial, 6-week duration
Participants	90 men (aged 18-55 years) randomised. Inclusion criteria: taking stable dose of an SSRI with substance-induced sexual dysfunction for more than 4 weeks; DSM-IV major depressive disorder in remission; HAM-A score < 11; HAM-D score < 11
Interventions	1. Sildenafil 50 mg, as required, increasing to 100 mg, as required, in addition to SSRI, or 2. Placebo in addition to SSRI
Outcomes	IIEF, ASEX, MGH-SFQ, HAM-D
Notes	Trial performed in USA - 3 centres

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Developed an unrestricted computer-generated randomisation schedule using SPSS version 10
Allocation concealment (selection bias)	Low risk	Randomisation schedule was given to an independent pharmacy. Medications were sealed in sequentially-numbered, identical containers according to allocation sequence
Blinding (performance bias and detection bias) All outcomes	Low risk	All study personnel and patents were blinded to treatment for the duration of the study
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All study personnel and patents were blinded to treatment for the duration of the study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All study personnel and patents were blinded to treatment for the duration of the study
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	-
Selective reporting (reporting bias)	Unclear risk	-

Safarinejad 2010

Methods	Parallel-group design, 12-week randomised phase
Participants	234 men (aged 25-50 years). Inclusion criteria: major depressive disorder currently in remission; stable dose of SSRI for at least 6 months; new sexual dysfunction for at least 4 weeks
Interventions	1. Bupropion SR 150 mg twice daily, or 2. Placebo
Outcomes	CGI-SF, IIEF, ASEX, Erectile Dysfunction Inventory of Treatment Satisfaction (patient and partner versions), HAM-D and HAM-A
Notes	Trial performed in Iran

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation number for assignment to treatment group was determined using random permuted blocks
Allocation concealment (selection bias)	Unclear risk	-
Blinding (performance bias and detection bias) All outcomes	Low risk	'Double blind'
Blinding of participants and personnel (performance bias) All outcomes	Low risk	'Double blind'
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Investigator was not involved in the recruitment procedure and did not know the randomisation list. Seals were broken after the trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Unclear risk	-

Safarinejad 2011

Methods	Parallel-group design, 12 weeks of randomised treatment after 1 week placebo run-in
Participants	218 women (aged 25-45). Inclusion criteria: SSRI-induced sexual dysfunction; first episode of major depressive disorder in remission
Interventions	1. Bupropion SR 150 mg twice daily, or 2. Placebo
Outcomes	CGI-SF, Female Sexual Function Index, HAM-D
Notes	Trial performed in Iran

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated schedule
Allocation concealment (selection bias)	Unclear risk	-
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	-
Selective reporting (reporting bias)	Unclear risk	-

Wheatley 2004

Methods	Triple-blind, parallel-arm design. 12 weeks of treatment after 1 week run-in without treatment
Participants	24 adults randomised (14 men, 10 women), aged 18-65 years. Inclusion criteria: taking antidepressant for at least 2 weeks and experiencing sexual problems as a consequence

Wheatley 2004 (*Continued*)

Interventions	1. *Ginkgo biloba* (LI-156) 240 mg daily, or 2. Placebo daily	
Outcomes	Changes in sexual dysfunction scale, ASEX, University of Mexico Sexual Function Inventory	
Notes	Trial performed in the UK	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated schedule
Allocation concealment (selection bias)	Unclear risk	-
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Allocation blinded to participant, investigator and statistician
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Allocation blinded to participant, investigator and statistician
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	-
Incomplete outcome data (attrition bias) All outcomes	Low risk	-
Selective reporting (reporting bias)	Unclear risk	-

Abbreviations
< = less than
> = more than
ASEX = Arizona Sexual Experiences scale
BISF-W = Brief Index of Sexual Functioning for Women
CGI = Clinical Global Impression scale
CGI-SF = Clinical Global Impression scale for Sexual Function
CSFQ = Changes in Sexual Functioning Questionnaire
DSM-III-R = Diagnostic and Statistical Manual of American Psychiatric Association, third edition, revised
DSM-IV = Diagnostic and Statistical Manual of American Psychiatric Association, fourth edition
FSFSQ = Feiger Sexual Function and Satisfaction Questionnaire
h = hour(s)
HAM-A = Hamilton rating scale for anxiety
HAM-D = Hamilton rating scale for depression

IIEF = International Index of Erectile Function
MGH-SFQ = Massachusetts General Hospital-Sexual Function Questionnaire
MINI = Mini-Mental State Examination
SEP diary = Sexual Encounter Profile diary
SR = sustained release
SRI = Serotonin Reuptake Inhibitor
SSES = Sexual Side Effects Scale
SSRI = Selective Serotonin Reuptake Inhibitor
VAS = Visual Analogue Scale
UKU = Udvalg fur Kliniske Undersogelser

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Aizenberg 2003	Non-randomised design
Amiaz 2011	Not established as antidepressant-induced sexual dysfunction: depressed men, also hypogonadal (low or low-normal testosterone levels)
Ashton 1998	Non-randomised design
Berk 2000	Non-randomised design
Cohen 1999	Non-randomised design
Dording 2012	Not established as antidepressant-induced sexual dysfunction: changes in sexual dysfunction ratings during treatment for resistant depression
Gelenberg 2000	Non-randomised design
Landen 1999	Not established as antidepressant-induced sexual dysfunction: changes in sexual dysfunction ratings during treatment for resistant depression
Mansoori 2011	Not a study of sexual dysfunction effects (safety evaluation)
Moore 2002	Review article
Nurnberg 2001	Pooled analysis of subgroup data from multiple individual studies; participants taking antidepressant medication, but not established as antidepressant-induced sexual dysfunction
Ozmenler 2008	Non-randomised design
Pae 2009	Not established as antidepressant-induced sexual dysfunction: changes in sexual dysfunction ratings during treatment for resistant depression
Salerian 2000	Non-randomised design

(*Continued*)

Salerian 2002	Non-randomised design
Segraves 2007	Pooled analysis of subgroup data from multiple individual studies; participants taking antidepressant medication, but not established as antidepressant-induced sexual dysfunction
Tignol 2004	Not established as antidepressant-induced sexual dysfunction: persistent erectile dysfunction after depression was brought into remission with or without antidepressant medication
Walker 1993	Non-randomised design
Worthington 2002	Non-randomised design

Characteristics of studies awaiting assessment *[ordered by study ID]*

Croft 2012

Methods	Randomized allocation
Participants	Women, aged 18-50 years. Inclusion criteria: mild or remitted depressive disorder; SSRI or SNRI; decreased sexual desire and distress present for at least 4 weeks
Interventions	1. Flibanserin, or 2. Placebo
Outcomes	
Notes	

Kashani 2013

Methods	Random allocation
Participants	38 women. Inclusion criteria: major depression; stabilized on fluoxetine 40 mg/day for a minimum of 6 weeks; had experienced subjective feeling of sexual dysfunction
Interventions	1. Saffron (30 mg/daily), for 4 weeks, or 2. Placebo for 4 weeks
Outcomes	FSFI
Notes	

MGH 2013

Methods	Randomised allocation
Participants	Women, aged 45-65 years. Inclusion criteria: post-menopause; persistent depression despite SSRI treatment
Interventions	1. Testosterone cream, or 2. Placebo
Outcomes	
Notes	Study title 'Testosterone Antidepressant Augmentation in Women'

Modabbernia 2012

Methods	Randomised, double-blind, placebo-controlled study
Participants	36 men Inclusion criteria: major depressive disorder; depressive symptoms stabilized on fluoxetine; subjective complaints of sexual impairment
Interventions	1. Saffron (15 mg twice per day) for 4 weeks, or 2. Placebo for 4 weeks
Outcomes	IIEF scale
Notes	

Abbreviations
IIEF = International Index of Erectile Function
SSRI = Selective Serotonin Reuptake Inhibitor

Characteristics of ongoing studies *[ordered by study ID]*

Chiang 2010

Trial name or title	Trazodone for SSRI-SD in Civilian Administration Division of Beitou Armed Forces Hospital
Methods	Randomized, placebo-control. cross-over design, 6-week duration
Participants	Inclusion criteria: participants 20-65 years of age; receiving SSRI treatment for > 4 weeks; minimal dose of fluoxetine, paroxetine, and citalopram 20 mg/day; minimal dose of fluvoxamine and sertraline 50 mg/day; and minimal dose of escitalopram 10 mg/day; developing sexual dysfunction based on the definition of ASEX Chinese version
Interventions	1. Trazodone 50 mg/day titrated to 100 mg/day over 1 week, then maintained, or 2. Placebo

Chiang 2010 (*Continued*)

Outcomes	Primary outcomes: differences between trazodone and placebo in the ASEX Chinese version at the end of week 6 Secondary outcomes assessed include: difference between trazodone and placebo in the CGI scale, 10-point VAS, HAM-D, and HAM-A at the end of week 6. Relationships between 5-HT2A polymorphism and changes in ASEX Chinese version also evaluated
Starting date	2010
Contact information	Kuo-Tung Chiang, MD
Notes	

Dording 2010

Trial name or title	A double-blind, placebo-controlled study of maca root for the treatment of antidepressant-induced sexual dysfunction in women
Methods	Randomized. 12-week duration
Participants	Women, 18-80 years
Interventions	1. Maca root 3 g/day, or 2. Placebo
Outcomes	Decrease in baseline ASEX and MGH-Sexual Dysfunction scores
Starting date	2007
Contact information	Christina Dording, MD, Massachussetts General Hospital
Notes	

Hellerstein 2008

Trial name or title	Treatment of sexual dysfunction secondary to antidepressant pharmacotherapy: a double-blind comparison of Requip (Ropinirole) vs placebo in patients taking SSRI antidepressants
Methods	Randomized, cross-over trial, 6- week duration
Participants	Inclusion criteria: male or female outpatients, 18-65 years old; currently taking fluoxetine, sertraline, paroxetine, citalopram, or escitalopram at a stable dosage within the ranges specified for 1 month or longer; required dosage range: (Prozac (fluoxetine) 20-80 mg/day; Celexa (citalopram) 20-60 mg/day; Lexapro (escitalopram) 10-30 mg/day; Zoloft (sertraline) 50-200 mg/day; Paxil (paroxetine) 20-60 mg/day; Paxil CR (paroxetine CR) 25-75 mg/day; currently responding to SSRI antidepressant treatment, as indicated by a score of 15 or less on the HAM-D 24-item at screening and baseline, and (b) CGI-Severity score of 2 or less at baseline; meets DSM-IV criteria for Substance-Induced Sexual Dysfunction, with impairment of desire, arousal, or orgasm; currently involved in an intimate relationship that includes sexual contact; agree to use double-barrier

Hellerstein 2008 (*Continued*)

	contraception during sexual intercourse during the course of the study (women only); agree to let the study team contact the physician who prescribed the SSRI medication to inform him/her of patient's participation in the current study
Interventions	1. Ropinirole 1 mg extended release formulation given once/day to a maximum of 4/day 2. placebo
Outcomes	Primary outcomes: IIEF, SFSQ Secondary outcomes: HAM-D 17-items, GAFS, CGI, CGI-SF
Starting date	2006
Contact information	David J Hellerstein, MD St. Luke's Roosevelt Hospital Center and NY State Psychiatric Institute
Notes	

Meston 2008

Trial name or title	*Ginkgo Biloba*: Antidepressant-Induced Sexual Dysfunction
Methods	Parallel-group design
Participants	36 women (age 18-65 years). Inclusion criteria: stabilised on antidepressant medication and free of a current Axis I disorder
Interventions	1. *Ginkgo biloba* extract 200 mg for 8 weeks, or 2. Placebo for 8 weeks
Outcomes	Daily participant diary, participant-rating scales, blind independent evaluator ratings, vaginal photoplethysmography
Starting date	June 2002
Contact information	Cindy Meston, University of Texas at Austin
Notes	Outcomes for those with antidepressant-associated sexual dysfunction not yet published

Takeda 2011

Trial name or title	A randomised, double-blind, parallel-group, active-controlled, flexible-dose study evaluating the effect of Lu AA21004 vs escitalopram on sexual functioning in adults with well-treated major depressive disorder experiencing selective serotonin reuptake inhibitor-induced sexual dysfunction
Methods	Randomised; parallel-group design; blinding applied to subjects, caregivers, investigators, outcomes assessors, 8-week treatment duration

Takeda 2011 (*Continued*)

Participants	Estimated enrolment: 440, aged 18-55 years; male and female participants Inclusion criteria: treated for last 8 weeks, or more, with SSRI monotherapy (only citalopram, paroxetine, or sertraline allowed) prescribed to treat a major depressive episode, according to the DSM-IV-TR criteria; depression currently stable; subject has a CGI Scale-Severity of Illness Scale (CGI-S) score of ≤ 3; currently experiencing treatment-emergent sexual dysfunction (defined as a CSFQ-14 total score ≤ 41 for women and ≤ 47 for men); considered to be attributable to the current SSRI monotherapy; suitable for a switch in medication
Interventions	1. Lu AA21004 up to 20 mg daily, or 2. Escitalopram up to 20 mg daily
Outcomes	Primary outcome: change from baseline in the CSFQ-14 Total Score
Starting date	June 2011
Contact information	Contact: Takeda Study Registration Call Center
Notes	62 study locations in USA and Canada Lu AA21004 is also known as vortioxetine

Van Rooiji 2010

Trial name or title	Lybrido(s) and SSRIs @Home: a double-blind, randomised, cross-over, placebo-controlled study to investigate the subjective and physiological efficacy and safety of Lybrido and Lybridos in the domestic setting in healthy women with female sexual dysfunction in combination with SSRI use. - @HOME
Methods	Cross-over design in which a placebo regime (duration 4 weeks), the Lybrido regime (duration 4 weeks), and the Lybridos regime (duration 4 weeks) are separated by a 1- to 4-week washout period
Participants	Target sample size: 40 Inclusion criteria: women 21-70 years old with hypoactive sexual desire disorder (comorbidity with other sexual dysfunctions e.g. Female Sexual Arousal Disorder (FSAD) allowed) or SSRI-induced sexual dysfunctioning, or both; at least 3 months use of an SSRI; SSRI must be on a stable dose for at least 6 weeks
Interventions	1. Lybrido [combination testosterone and sildenafil], or 2. Lybridos [combination testosterone and buspirone], or 3. Placebo
Outcomes	Unclear
Starting date	January 2010
Contact information	Emotional Brain bv, Louis Armstrongweg 78 1311 RL Almere The Netherlands

Notes	

Abbreviations
≤ = less than or equal to
> = more than
ASEX = Arizona Sexual Experiences scale
CGI = Clinical Global Impression scale
CGI-SF = Clinical Global Impression scale for Sexual Function
CSFQ = Changes in Sexual Functioning Questionnaire
DSM-IV = Diagnostic and Statistical Manual of American Psychiatric Association, fourth edition
DSM-IV-TR = Diagnostic and Statistical Manual of American Psychiatric Association, fourth edition, text revision
FSFI = Female sSexual Function Index
GAFS = Global Assessment of Functioning Scale
HAM-D = Hamilton rating scale for depression
IIEF = International Index of Erectile Function
MGH = Massachusetts General Hospital
SFSQ = Sexual Function Satisfaction Questionnaire
SNRI = Serotonin-Norepinephrine Reuptake Inhibitor
SSRI = Selective Serotonin Reuptake Inhibitor
VAS = Visual Analogue Scale

DATA AND ANALYSES

Comparison 1. Sildenafil vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Endpoint International Index of Erectile Function (IIEF) scores	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Total score	2	112	Mean Difference (IV, Fixed, 95% CI)	19.36 [15.00, 23.72]
1.2 Erectile function (questions 1-5,15)	1	89	Mean Difference (IV, Fixed, 95% CI)	10.0 [7.39, 12.61]
1.3 Question 3: ability to achieve erection	2	231	Mean Difference (IV, Fixed, 95% CI)	1.04 [0.65, 1.44]
1.4 Question 4: ability to maintain erection	2	231	Mean Difference (IV, Fixed, 95% CI)	1.18 [0.78, 1.59]
1.5 Intercourse satisfaction (questions 6, 7, 8)	1	89	Mean Difference (IV, Fixed, 95% CI)	3.50 [2.48, 4.52]
1.6 Orgasmic function (questions 9, 10)	1	89	Mean Difference (IV, Fixed, 95% CI)	2.5 [1.36, 3.64]
1.7 Sexual desire (questions 11, 12)	1	89	Mean Difference (IV, Fixed, 95% CI)	0.5 [-0.38, 1.38]
1.8 Overall satisfaction (questions 13,14)	1	89	Mean Difference (IV, Fixed, 95% CI)	1.80 [0.86, 2.74]
2 Endpoint Erectile Dysfunction Inventory of Treatment Satisfaction (EDITS) scores	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 Total score	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Endpoint Clinical Global Impression - Sexual Function	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4 Clinical Global Impression -Sexual Function not "much/very much improved" by endpoint	2	187	Risk Ratio (M-H, Fixed, 95% CI)	0.44 [0.33, 0.58]
4.1 Males	1	89	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.34, 0.66]
4.2 Females	1	98	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.24, 0.62]
5 Endpoint Arizona Sexual Experience Scale (ASEX) total scores	3	210	Mean Difference (IV, Fixed, 95% CI)	-2.65 [-3.86, -1.44]
5.1 Males	2	112	Mean Difference (IV, Fixed, 95% CI)	-4.62 [-6.29, -2.95]
5.2 Females	1	98	Mean Difference (IV, Fixed, 95% CI)	-0.5 [-2.24, 1.24]
6 Males: endpoint Arizona Sexual Experience Scale scores	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6.1 Total score	2	112	Mean Difference (IV, Fixed, 95% CI)	-4.62 [-6.29, -2.95]
6.2 Sexual desire	1	89	Mean Difference (IV, Fixed, 95% CI)	-0.60 [-1.08, -0.12]
6.3 Arousal	1	89	Mean Difference (IV, Fixed, 95% CI)	-0.60 [-1.06, -0.14]
6.4 Erectile function	1	89	Mean Difference (IV, Fixed, 95% CI)	-1.20 [-1.66, -0.74]
6.5 Orgasm (ability)	1	89	Mean Difference (IV, Fixed, 95% CI)	-1.40 [-1.90, -0.90]
6.6 Orgasm (satisfaction)	1	89	Mean Difference (IV, Fixed, 95% CI)	-1.0 [-1.58, -0.42]

7 Endpoint MGH-Sexual Functioning Questionnaire scores	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7.1 Total score	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.2 Sexual desire	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.3 Arousal	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.4 Erectile function	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.5 Orgasm (ability)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.6 Overall satisfaction	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Sexual dysfunction defined by Arizona Sexual Experience Scale at trial endpoint	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
9 Dropouts	4	353	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.41, 1.14]
10 Endpoint Hamilton Rating Scale for Depression score	2	187	Mean Difference (IV, Fixed, 95% CI)	-0.94 [-1.94, 0.07]
11 Loss of remission: Hamilton Rating Scale for Depression score > 9	3	330	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.04, 3.09]
12 Global Efficacy Questionnaire (questions 1 & 2)	1	284	Risk Ratio (M-H, Fixed, 95% CI)	2.53 [1.90, 3.35]
12.1 Improvement in erections	1	142	Risk Ratio (M-H, Fixed, 95% CI)	2.5 [1.67, 3.73]
12.2 Improvement in ability to have sexual intercourse	1	142	Risk Ratio (M-H, Fixed, 95% CI)	2.55 [1.71, 3.80]
13 Global efficacy questionnaire (question 3)	1	129	Mean Difference (IV, Fixed, 95% CI)	1.2 [0.65, 1.75]
13.1 Question 3: Frequency of erection that allowed satisfactory sexual intercourse	1	129	Mean Difference (IV, Fixed, 95% CI)	1.2 [0.65, 1.75]
14 Endpoint Sexual Function Questionnaire (SFQ)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
14.1 Desire	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
14.2 Arousal-sensation	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
14.3 Arousal-lubrication	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
14.4 Orgasm	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
14.5 Enjoyment	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
14.6 Pain	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
14.7 Partner	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
15 UNM Sexual Function Inventory	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
15.1 Total score	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
15.2 Desire	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
15.3 Sexual arousal	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
15.4 Lubrication	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
15.5 Ability to reach orgasm	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
15.6 Overall satisfaction	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
16 Females: endpoint Arizona Sexual Experience Scale scores	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
16.1 Total score	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
16.2 Sexual desire	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
16.3 Arousal	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
16.4 Orgasm (ability)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

16.5 Orgasm (satisfaction)	1	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
16.6 Lubrication	1	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 2. Tadalafil vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Global Assessment Questions	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Has the treatment you have been taking improved your erectile function?	1	50	Risk Ratio (M-H, Fixed, 95% CI)	11.5 [3.03, 43.67]
1.2 Has the treatment improved your ability to engage in sexual activity?	1	50	Risk Ratio (M-H, Fixed, 95% CI)	11.5 [3.03, 43.67]
2 Endpoint Sexual Encounter Profile (SEP)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Question 2: Were you able to insert your penis into your partner's vagina?	1	50	Risk Ratio (M-H, Fixed, 95% CI)	2.33 [0.68, 8.01]
2.2 Question 3: Did your erection last long enough for you to have successful intercourse?	1	50	Risk Ratio (M-H, Fixed, 95% CI)	6.0 [0.78, 46.29]
2.3 Question 4: Were you satisfied with the hardness of your erection?	1	50	Risk Ratio (M-H, Fixed, 95% CI)	6.0 [0.78, 46.29]
2.4 Question 5: Were you satisfied overall with this sexual experience?	1	50	Risk Ratio (M-H, Fixed, 95% CI)	6.0 [0.78, 46.29]
3 Dropouts	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Overall	1	54	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.04, 3.24]
3.2 Lack of efficacy	1	54	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.04, 3.24]
3.3 Adverse effects	1	54	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 3. Bupropion vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Endpoint scale total scores	3	482	Std. Mean Difference (IV, Fixed, 95% CI)	1.60 [1.40, 1.81]
1.1 International Index of Erectile Function (IIEF)	1	227	Std. Mean Difference (IV, Fixed, 95% CI)	1.76 [1.45, 2.07]
1.2 Female Sexual Function Index (FSFI)	1	213	Std. Mean Difference (IV, Fixed, 95% CI)	1.73 [1.41, 2.05]

1.3 Changes in Sexual Functioning Questionnaire (CSFQ)	1	42	Std. Mean Difference (IV, Fixed, 95% CI)	0.50 [-0.11, 1.12]
2 Response (as defined by study)	3	284	Risk Ratio (M-H, Fixed, 95% CI)	31.77 [10.10, 99.89]
2.1 50% reduction Arizona Sexual Experiences Scale (ASEX)	2	71	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.09, 4.41]
2.2 Clinical Global Impression (CGI-SF) 2-point improvement	1	213	Risk Ratio (M-H, Fixed, 95% CI)	186.73 [11.74, 2969.23]
3 Endpoint International Index of Erectile Function (IIEF)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 Total score	1	227	Mean Difference (IV, Fixed, 95% CI)	20.10 [17.14, 23.06]
3.2 Erectile function	1	227	Mean Difference (IV, Fixed, 95% CI)	9.30 [8.18, 10.42]
3.3 Orgasmic function	1	227	Mean Difference (IV, Fixed, 95% CI)	2.70 [2.15, 3.25]
3.4 Sexual desire	1	227	Mean Difference (IV, Fixed, 95% CI)	2.10 [1.76, 2.44]
3.5 Intercourse satisfaction	1	227	Mean Difference (IV, Fixed, 95% CI)	3.6 [3.00, 4.20]
3.6 Overall satisfaction	1	227	Mean Difference (IV, Fixed, 95% CI)	2.60 [1.99, 3.21]
4 Endpoint Female Sexual Function Index score	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.1 Total score	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 Desire	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.3 Arousal	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.4 Lubrication	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.5 Orgasm	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.6 Satisfaction	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.7 Pain	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Endpoint Changes in Sexual Functioning Questionnaire score	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.1 Total score	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 Desire/interest	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.3 Desire/frequency	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.4 Arousal/excitement	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.5 Completion/orgasm	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Dropouts	5	579	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.67, 1.72]
7 Endpoint Hamilton Rating Scale for Depression score	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
8 Endpoint Clinical Global Impression (CGI - SF)	2	440	Mean Difference (IV, Fixed, 95% CI)	-1.74 [-1.87, -1.61]
8.1 Male	1	227	Mean Difference (IV, Fixed, 95% CI)	-1.5 [-1.80, -1.20]
8.2 Female	1	213	Mean Difference (IV, Fixed, 95% CI)	-1.80 [-1.95, -1.65]
9 Endpoint ASEX	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
9.1 Total score	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.2 Erectile function	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.3 Sexual desire	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.4 Arousal	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.5 Ability to reach orgasm	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.6 Satisfaction with orgasm	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
10 Endpoint EDITS (participant)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
10.1 Total score	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.2 Overall satisfaction	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

10.3 Expectations	1	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.4 Likelihood of continuing	1	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.5 Confidence	1	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.6 Partner satisfaction	1	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.7 Partner desire to continue treatment	1	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.8 Naturalness of achieving erection	1	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.9 Naturalness of erection hardness	1	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.10 Quickness of achieving erection	1	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.11 Duration that erection lasts	1	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.12 Ease of use	1	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
11 Endpoint EDITS (partner)	1	Mean Difference (IV, Fixed, 95% CI)	Totals not selected
11.1 Total score	1	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.2 Overall satisfaction	1	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.3 Expectations	1	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.4 Sexual desirability	1	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.5 Participant's feelings about continuing treatment	1	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.6 Duration that erection lasts	1	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 4. Nefazodone vs sertraline

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Re-emergence of antidepressant-induced sexual dysfunction (physician rated)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Week 1	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Endpoint	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Overall degree of sexual satisfaction (participant rated)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 Baseline	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Week 8	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 Last rating recorded	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Dropouts	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1 Overall	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Attributed to adverse effects	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Hamilton Rating Scale for Depression score	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.1 Baseline	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 Week 8	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 5. Ginkgo biloba vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Endpoint sexual function ratings (investigator questionnaire)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1 Sexual desire	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Overall sexual function	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Erection maintenance time	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.4 Orgasm frequency	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.5 Satisfaction to orgasm	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Sexual Dysfunction Scale (investigator developed)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 Baseline	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Week 12	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Dropouts	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 6. Granisetron vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change from baseline on Sexual Side Effects Scale (SSES) total score	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2 Endpoint Feiger Sexual Function and Satisfaction Questionnaire score	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 Total score	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Item 1	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 Item 2	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.4 Item 3	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.5 Item 4	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.6 Item 5	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.7 Item 6	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Endpoint Arizona Sexual Experience Scale (ASEX) score	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.1 Total score	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Sexual desire	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.3 Arousal	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.4 Lubrication	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.5 Orgasm (ability)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.6 Orgasm (satisfaction)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Dropouts	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5 Recurrence of mood symptoms	1	43	Risk Ratio (M-H, Fixed, 95% CI)	2.87 [0.12, 66.75]

Comparison 7. VML-670 vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Absence of sexual dysfunction at end point	1	266	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [0.86, 1.77]
2 'Improved' or 'much improved' on Clinical Global Impression	1	266	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [0.71, 2.17]
3 Change in Arizona Sexual Experiences Scale (ASEX) item scores	1	1264	Mean Difference (IV, Fixed, 95% CI)	-0.07 [-0.19, 0.05]
3.1 How strong is your sexual drive?	1	255	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.36, 0.16]
3.2 How easily are you sexually aroused?	1	253	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-0.47, 0.07]
3.3 Females: how easily does your vagina become moist or wet?	1	180	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.22, 0.42]
3.4 Males: can you easily get and keep an erection?	1	72	Mean Difference (IV, Fixed, 95% CI)	-0.4 [-0.80, 0.00]
3.5 How easily can you reach orgasm?	1	252	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.28, 0.28]
3.6 Are your orgasms satisfying?	1	252	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.22, 0.42]
4 Dropouts	1	532	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.73, 1.93]
4.1 Total	1	266	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.56, 1.68]
4.2 Attributed to adverse effects	1	266	Risk Ratio (M-H, Fixed, 95% CI)	2.32 [0.75, 7.21]

Comparison 8. Buspirone vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in patient-rated visual analogue scales	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Overall function (total of interest, lubrication, orgasm, pleasure)	1	39	Mean Difference (IV, Fixed, 95% CI)	3.10 [-38.33, 44.53]
1.2 Mood	1	39	Mean Difference (IV, Fixed, 95% CI)	0.80 [-7.61, 9.21]
1.3 Energy	1	39	Mean Difference (IV, Fixed, 95% CI)	5.30 [-3.88, 14.48]
1.4 Interest/desire	1	39	Mean Difference (IV, Fixed, 95% CI)	2.70 [-7.99, 13.39]
1.5 Lubrication	1	39	Mean Difference (IV, Fixed, 95% CI)	9.90 [-3.65, 23.45]
1.6 Orgasm	1	39	Mean Difference (IV, Fixed, 95% CI)	-6.3 [-19.98, 7.38]
1.7 Pleasure	1	39	Mean Difference (IV, Fixed, 95% CI)	-3.20 [-15.53, 9.13]
1.8 Discomfort	1	39	Mean Difference (IV, Fixed, 95% CI)	7.00 [-3.15, 17.15]
2 Dropouts	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 9. Bethanecol vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Visual analogue scale of orgasmic function - best score achieved	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Comparison 10. Olanzapine vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in patient rated assessment of sexual function	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1 Overall satisfaction	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Sexual interest	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Psychological arousal	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.4 Lubrication	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.5 Orgasm	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Change in diary ratings (visual analogue scales)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 Overall sexual function	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Mood	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 Energy	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.4 Sexual interest	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.5 Psychological arousal	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.6 Physical arousal	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.7 Orgasm	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.8 Pleasure/enjoyment	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.9 Discomfort	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Dropouts due to adverse effects	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 11. Mirtazapine vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in patient rated assessment of sexual function	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1 Overall satisfaction	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Sexual interest	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Psychological arousal	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.4 Lubrication	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.5 Orgasm	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

2 Change in diary ratings (visual analogue scales)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 Overall sexual function	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Mood	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 Energy	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.4 Sexual interest	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.5 Psychological arousal	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.6 Physical arousal	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.7 Orgasm	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.8 Pleasure/enjoyment	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.9 Discomfort	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Endpoint modified Kinsey Structured Interview	1	75	Mean Difference (IV, Fixed, 95% CI)	0.60 [0.19, 1.01]
3.1 Sexual satisfaction	1	75	Mean Difference (IV, Fixed, 95% CI)	0.60 [0.19, 1.01]
4 Dropouts	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.1 Attributed to adverse effects	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 12. Yohimbine vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in patient rated assessment of sexual function	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1 Overall satisfaction	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Sexual interest	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Psychological arousal	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.4 Lubrication	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.5 Orgasm	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Change in diary ratings (visual analogue scales)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 Overall sexual function	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Mood	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 Energy	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.4 Sexual interest	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.5 Psychological arousal	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.6 Physical arousal	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.7 Orgasm	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.8 Pleasure/enjoyment	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.9 Discomfort	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Dropouts	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1 Attributed to adverse effects	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 13. Amantadine vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in patient-rated visual analogue scales	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Overall function (total of interest, lubrication, orgasm, pleasure)	1	38	Mean Difference (IV, Fixed, 95% CI)	13.0 [-29.02, 55.02]
1.2 Mood	1	38	Mean Difference (IV, Fixed, 95% CI)	8.1 [1.23, 14.97]
1.3 Energy	1	38	Mean Difference (IV, Fixed, 95% CI)	12.7 [5.30, 20.10]
1.4 Interest/desire	1	38	Mean Difference (IV, Fixed, 95% CI)	0.90 [-7.96, 9.76]
1.5 Lubrication	1	38	Mean Difference (IV, Fixed, 95% CI)	7.90 [-5.74, 21.54]
1.6 Orgasm	1	38	Mean Difference (IV, Fixed, 95% CI)	2.50 [-11.91, 16.91]
1.7 Pleasure	1	38	Mean Difference (IV, Fixed, 95% CI)	1.70 [-11.28, 14.68]
1.8 Discomfort	1	38	Mean Difference (IV, Fixed, 95% CI)	1.30 [-11.25, 13.85]
2 Dropouts	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 14. ephedrine vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Endpoint Brief Index of Sexual Functioning for Women (BISF-W)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1 Sexual desire	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Sexual arousability	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Lack of vaginal lubrication	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.4 Orgasm ability	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.5 Orgasm intensity/pleasure	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.6 Sexual dissatisfaction	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 15. Maca root: high vs low dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Endpoint Arizona Sexual Experiences Scale (ASEX) score	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1 Total score	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Question 1: Sexual desire	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Endpoint MGH-SFQ	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 Total score	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Item a: Sexual desire	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

3 Dropouts	1	20	Risk Ratio (M-H, Fixed, 95% CI)	1.5 [0.60, 3.74]
4 Endpoint ratings of psychiatric symptoms	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 Hamilton Depression Rating Scale	1	16	Mean Difference (IV, Fixed, 95% CI)	-2.5 [-7.98, 2.98]
4.2 Hamilton Anxiety Rating Scale	1	16	Mean Difference (IV, Fixed, 95% CI)	-0.40 [-3.15, 2.35]

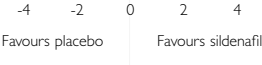
Analysis 1.1. Comparison 1 Sildenafil vs placebo, Outcome 1 Endpoint International Index of Erectile Function (IIEF) scores.

Review: Strategies for managing sexual dysfunction induced by antidepressant medication

Comparison: 1 Sildenafil vs placebo

Outcome: 1 Endpoint International Index of Erectile Function (IIEF) scores

Study or subgroup	Sildenafil N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Total score							
Ginsberg 2001	12	62.6 (14)	11	44.2 (15.7)		12.8 %	18.40 [6.20, 30.60]
Numberg 2003	44	60.4 (10.3)	45	40.9 (12.1)		87.2 %	19.50 [14.84, 24.16]
Subtotal (95% CI)	**56**		**56**			**100.0 %**	**19.36 [15.00, 23.72]**
Heterogeneity: Chi² = 0.03, df = 1 (P = 0.87); I² =0.0%							
Test for overall effect: Z = 8.71 (P < 0.00001)							
2 Erectile function (questions 1-5,15)							
Numberg 2003	44	27.1 (3.7)	45	17.1 (8.1)		100.0 %	10.00 [7.39, 12.61]
Subtotal (95% CI)	**44**		**45**			**100.0 %**	**10.00 [7.39, 12.61]**
Heterogeneity: not applicable							
Test for overall effect: Z = 7.52 (P < 0.00001)							
3 Question 3: ability to achieve erection							
Fava 2006	71	3.9 (1.69)	71	3.1 (1.69)		51.2 %	0.80 [0.24, 1.36]
Numberg 2003	44	4.4 (1.1)	45	3.1 (1.6)		48.8 %	1.30 [0.73, 1.87]
Subtotal (95% CI)	**115**		**116**			**100.0 %**	**1.04 [0.65, 1.44]**
Heterogeneity: Chi² = 1.52, df = 1 (P = 0.22); I² =34%							
Test for overall effect: Z = 5.14 (P < 0.00001)							
4 Question 4: ability to maintain erection							
Fava 2006	71	3.7 (1.69)	71	2.8 (1.69)		52.7 %	0.90 [0.34, 1.46]
Numberg 2003	44	4.2 (1.2)	45	2.7 (1.6)		47.3 %	1.50 [0.91, 2.09]
Subtotal (95% CI)	**115**		**116**			**100.0 %**	**1.18 [0.78, 1.59]**
Heterogeneity: Chi² = 2.12, df = 1 (P = 0.15); I² =53%							



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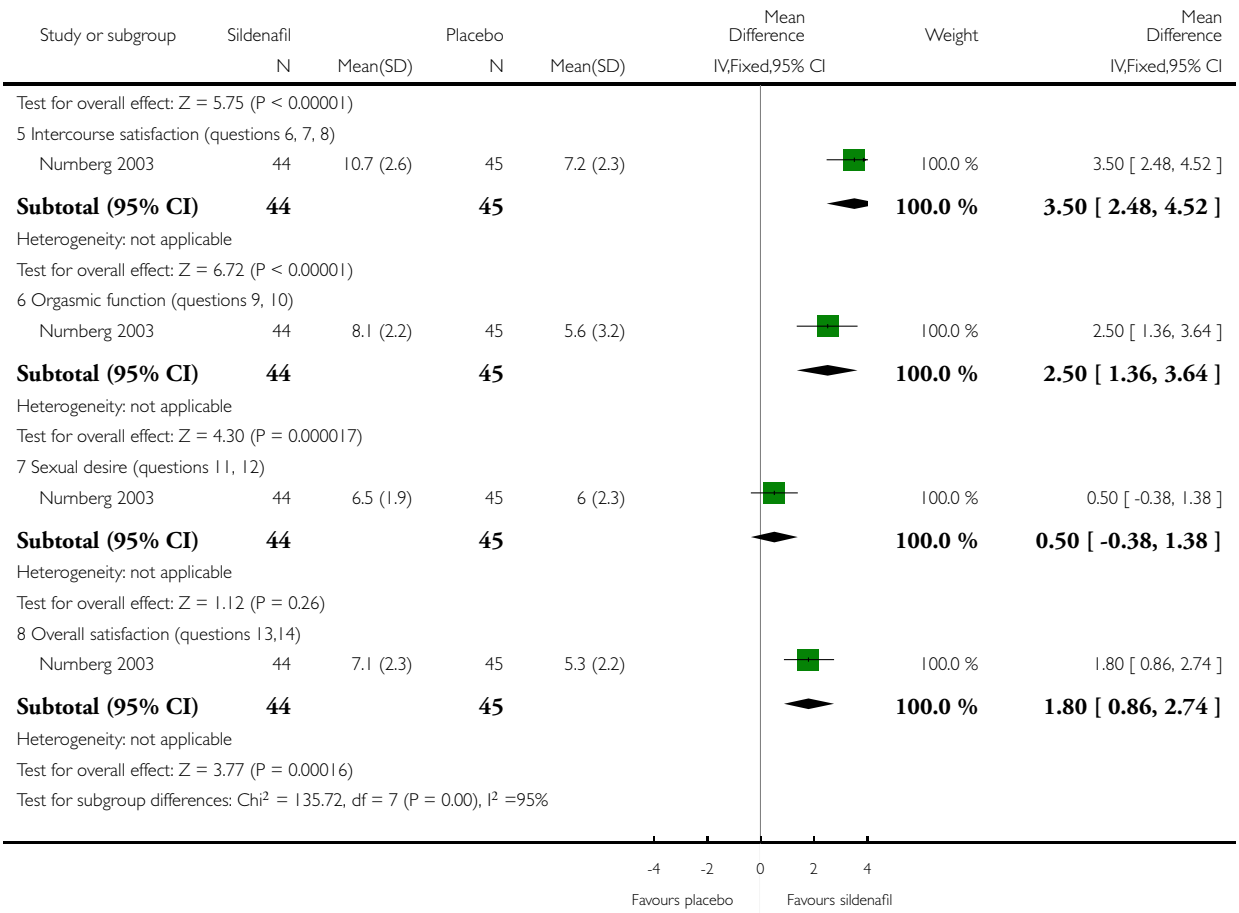


Analysis 1.2. Comparison 1 Sildenafil vs placebo, Outcome 2 Endpoint Erectile Dysfunction Inventory of Treatment Satisfaction (EDITS) scores.

Review: Strategies for managing sexual dysfunction induced by antidepressant medication

Comparison: 1 Sildenafil vs placebo

Outcome: 2 Endpoint Erectile Dysfunction Inventory of Treatment Satisfaction (EDITS) scores

Study or subgroup	Sildenafil N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Total score						
Ginsberg 2001	12	75.8 (20.3)	11	54.2 (21.9)		21.60 [4.30, 38.90]

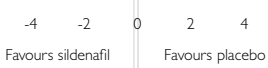
Analysis 1.3. Comparison 1 Sildenafil vs placebo, Outcome 3 Endpoint Clinical Global Impression - Sexual Function.

Review: Strategies for managing sexual dysfunction induced by antidepressant medication

Comparison: 1 Sildenafil vs placebo

Outcome: 3 Endpoint Clinical Global Impression - Sexual Function

Study or subgroup	Sildenafil N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Nurnberg 2008	49	2.8 (1.1)	49	3.6 (0.9)		-0.80 [-1.20, -0.40]



Analysis 1.4. Comparison 1 Sildenafil vs placebo, Outcome 4 Clinical Global Impression -Sexual Function not "much/very much improved" by endpoint.

Review: Strategies for managing sexual dysfunction induced by antidepressant medication

Comparison: 1 Sildenafil vs placebo

Outcome: 4 Clinical Global Impression -Sexual Function not "much/very much improved" by endpoint

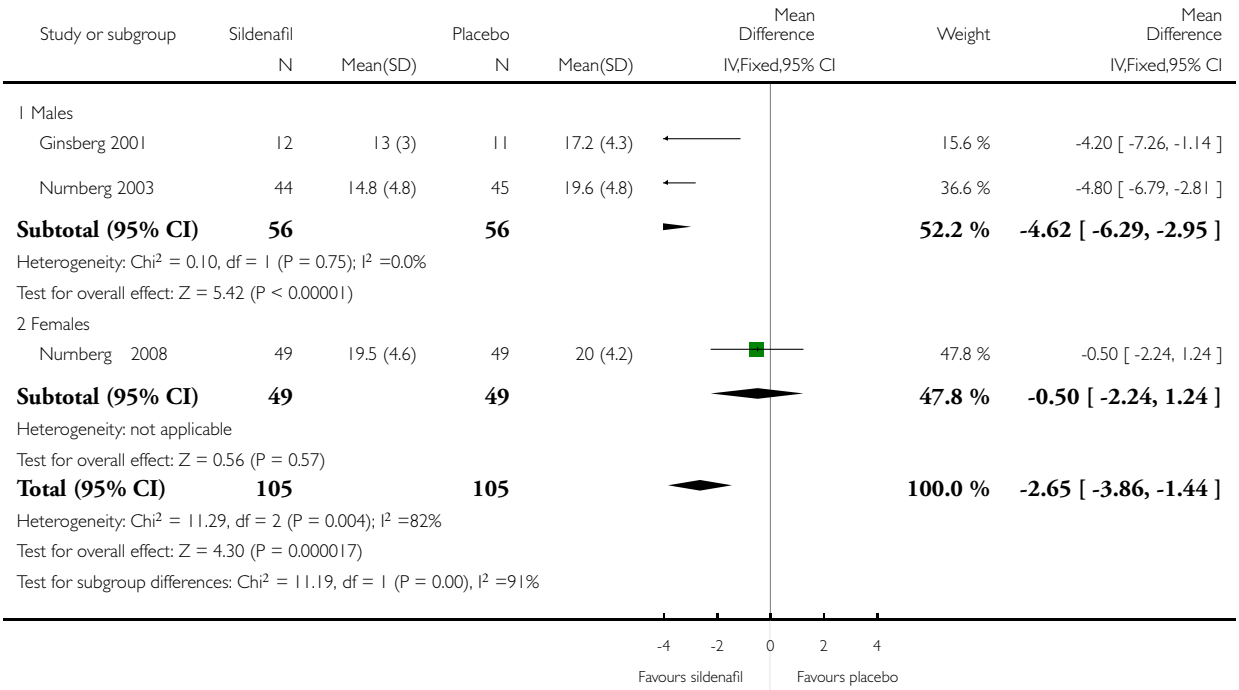
Study or subgroup	sildenafil n/N	placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Males					
Nurnberg 2003	20/44	43/45		54.1 %	0.48 [0.34, 0.66]
Subtotal (95% CI)	**44**	**45**		**54.1 %**	**0.48 [0.34, 0.66]**
Total events: 20 (sildenafil), 43 (placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 4.42 (P = 0.000010)					
2 Females					
Nurnberg 2008	14/49	36/49		45.9 %	0.39 [0.24, 0.62]
Subtotal (95% CI)	**49**	**49**		**45.9 %**	**0.39 [0.24, 0.62]**
Total events: 14 (sildenafil), 36 (placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.91 (P = 0.000093)					
Total (95% CI)	**93**	**94**		**100.0 %**	**0.44 [0.33, 0.58]**
Total events: 34 (sildenafil), 79 (placebo)					
Heterogeneity: Chi^2 = 0.49, df = 1 (P = 0.48); I^2 =0.0%					
Test for overall effect: Z = 5.87 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 0.47, df = 1 (P = 0.49), I^2 =0.0%					

Analysis 1.5. Comparison 1 Sildenafil vs placebo, Outcome 5 Endpoint Arizona Sexual Experience Scale (ASEX) total scores.

Review: Strategies for managing sexual dysfunction induced by antidepressant medication

Comparison: 1 Sildenafil vs placebo

Outcome: 5 Endpoint Arizona Sexual Experience Scale (ASEX) total scores

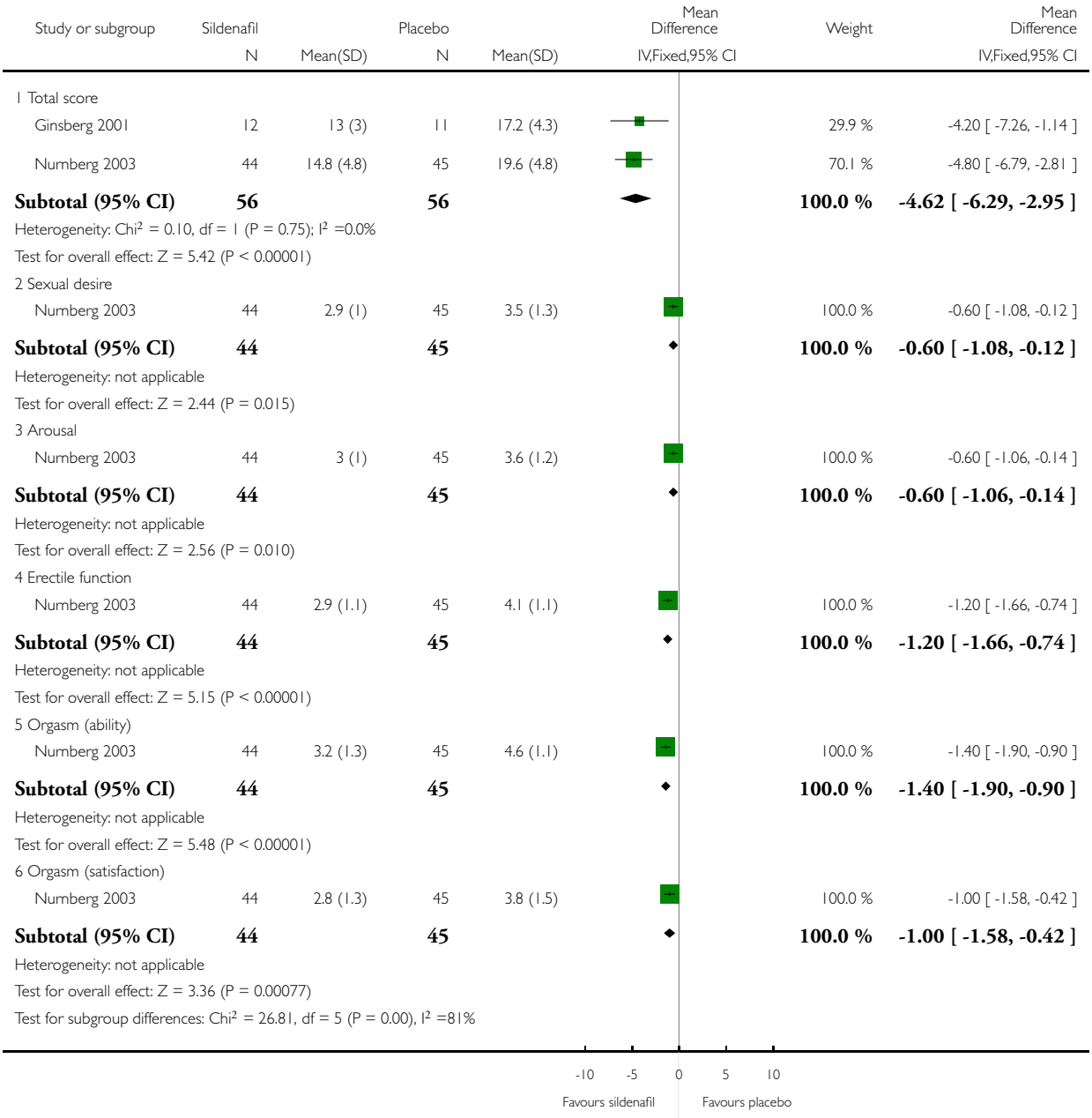


Analysis 1.6. Comparison 1 Sildenafil vs placebo, Outcome 6 Males: endpoint Arizona Sexual Experience Scale scores.

Review: Strategies for managing sexual dysfunction induced by antidepressant medication

Comparison: 1 Sildenafil vs placebo

Outcome: 6 Males: endpoint Arizona Sexual Experience Scale scores



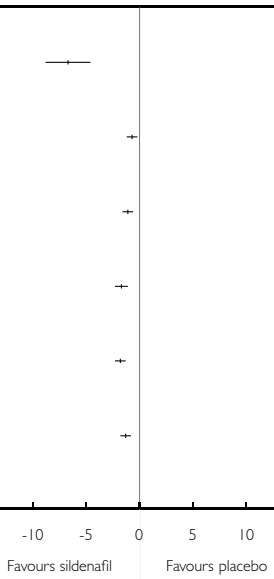
Analysis 1.7. Comparison 1 Sildenafil vs placebo, Outcome 7 Endpoint MGH-Sexual Functioning Questionnaire scores.

Review: Strategies for managing sexual dysfunction induced by antidepressant medication

Comparison: 1 Sildenafil vs placebo

Outcome: 7 Endpoint MGH-Sexual Functioning Questionnaire scores

Study or subgroup	Sildenafil N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Total score						
Numberg 2003	44	13.9 (5.7)	45	20.6 (4.3)		-6.70 [-8.80, -4.60]
2 Sexual desire						
Numberg 2003	44	2.5 (1.2)	45	3.2 (1.2)		-0.70 [-1.20, -0.20]
3 Arousal						
Numberg 2003	44	2.6 (1.3)	45	3.7 (1.3)		-1.10 [-1.64, -0.56]
4 Erectile function						
Numberg 2003	44	3.1 (1.6)	45	4.8 (1.2)		-1.70 [-2.29, -1.11]
5 Orgasm (ability)						
Numberg 2003	44	2.7 (1.3)	45	4.5 (1)		-1.80 [-2.28, -1.32]
6 Overall satisfaction						
Numberg 2003	44	3 (1.4)	45	4.3 (1)		-1.30 [-1.81, -0.79]



Analysis 1.8. Comparison 1 Sildenafil vs placebo, Outcome 8 Sexual dysfunction defined by Arizona Sexual Experience Scale at trial endpoint.

Review: Strategies for managing sexual dysfunction induced by antidepressant medication

Comparison: 1 Sildenafil vs placebo

Outcome: 8 Sexual dysfunction defined by Arizona Sexual Experience Scale at trial endpoint

Study or subgroup	Sildenafil n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Ginsberg 2001	1/11	5/10		0.18 [0.03, 1.30]

Analysis 1.9. Comparison 1 Sildenafil vs placebo, Outcome 9 Dropouts.

Review: Strategies for managing sexual dysfunction induced by antidepressant medication

Comparison: 1 Sildenafil vs placebo

Outcome: 9 Dropouts

Study or subgroup	Sildenafil n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Fava 2006	4/71	9/71		30.8 %	0.44 [0.14, 1.38]
Ginsberg 2001	3/12	4/11		14.3 %	0.69 [0.20, 2.41]
Numberg 2008	10/49	12/49		41.1 %	0.83 [0.40, 1.75]
Numberg 2003	3/45	4/45		13.7 %	0.75 [0.18, 3.16]
Total (95% CI)	**177**	**176**		**100.0 %**	**0.68 [0.41, 1.14]**

Total events: 20 (Sildenafil), 29 (Placebo)

Heterogeneity: $Chi^2 = 0.85$, df = 3 (P = 0.84); $I^2 = 0.0\%$

Test for overall effect: Z = 1.45 (P = 0.15)

Test for subgroup differences: Not applicable

Analysis 1.10. Comparison 1 Sildenafil vs placebo, Outcome 10 Endpoint Hamilton Rating Scale for Depression score.

Review: Strategies for managing sexual dysfunction induced by antidepressant medication

Comparison: 1 Sildenafil vs placebo

Outcome: 10 Endpoint Hamilton Rating Scale for Depression score

Study or subgroup	Sildenafil N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Numberg 2008	49	4 (3.5)	49	3.9 (3.6)		50.7 %	0.10 [-1.31, 1.51]
Numberg 2003	44	3.5 (2.9)	45	5.5 (3.9)		49.3 %	-2.00 [-3.43, -0.57]
Total (95% CI)	**93**		**94**			**100.0 %**	**-0.94 [-1.94, 0.07]**

Heterogeneity: $Chi^2 = 4.23$, df = 1 (P = 0.04); $I^2 = 76\%$

Test for overall effect: Z = 1.83 (P = 0.067)

Test for subgroup differences: Not applicable

Analysis 1.11. Comparison 1 Sildenafil vs placebo, Outcome 11 Loss of remission: Hamilton Rating Scale for Depression score > 9.

Review: Strategies for managing sexual dysfunction induced by antidepressant medication

Comparison: 1 Sildenafil vs placebo

Outcome: 11 Loss of remission: Hamilton Rating Scale for Depression score > 9

Study or subgroup	Sildenafil n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Fava 2006	0/71	0/71		0.0 [0.0, 0.0]
Nurnberg 2008	1/49	3/49		0.33 [0.04, 3.09]
Nurnberg 2003	0/45	0/45		0.0 [0.0, 0.0]
Total (95% CI)	**165**	**165**		**0.33 [0.04, 3.09]**

Total events: 1 (Sildenafil), 3 (Placebo)

Heterogeneity: $Chi^2 = 0.0$, df = 0 (P = 1.00); $I^2 = 0.0\%$

Test for overall effect: Z = 0.97 (P = 0.33)

Test for subgroup differences: Not applicable

Analysis 1.12. Comparison 1 Sildenafil vs placebo, Outcome 12 Global Efficacy Questionnaire (questions 1 & 2).

Review: Strategies for managing sexual dysfunction induced by antidepressant medication

Comparison: 1 Sildenafil vs placebo

Outcome: 12 Global Efficacy Questionnaire (questions 1 % 2)

Study or subgroup	Sildenafil n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Improvement in erections					
Fava 2006	50/71	20/71		50.0 %	2.50 [1.67, 3.73]
Subtotal (95% CI)	**71**	**71**		**50.0 %**	**2.50 [1.67, 3.73]**
Total events: 50 (Sildenafil), 20 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 4.48 (P < 0.00001)					
2 Improvement in ability to have sexual intercourse					
Fava 2006	51/71	20/71		50.0 %	2.55 [1.71, 3.80]
Subtotal (95% CI)	**71**	**71**		**50.0 %**	**2.55 [1.71, 3.80]**
Total events: 51 (Sildenafil), 20 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 4.60 (P < 0.00001)					
Total (95% CI)	**142**	**142**		**100.0 %**	**2.53 [1.90, 3.35]**
Total events: 101 (Sildenafil), 40 (Placebo)					
Heterogeneity: Chi^2 = 0.00, df = 1 (P = 0.95); I^2 =0.0%					
Test for overall effect: Z = 6.42 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 0.00, df = 1 (P = 0.95), I^2 =0.0%					

Analysis 1.13. Comparison 1 Sildenafil vs placebo, Outcome 13 Global efficacy questionnaire (question 3).

Review: Strategies for managing sexual dysfunction induced by antidepressant medication

Comparison: 1 Sildenafil vs placebo

Outcome: 13 Global efficacy questionnaire (question 3)

Study or subgroup	Sildenafil N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Question 3: Frequency of erection that allowed satisfactory sexual intercourse							
Fava 2006	67	2.5 (1.64)	62	1.3 (1.57)		100.0 %	1.20 [0.65, 1.75]
Total (95% CI)	**67**		**62**			**100.0 %**	**1.20 [0.65, 1.75]**

Heterogeneity: not applicable

Test for overall effect: Z = 4.25 (P = 0.000022)

Test for subgroup differences: Not applicable

Analysis 1.14. Comparison 1 Sildenafil vs placebo, Outcome 14 Endpoint Sexual Function Questionnaire (SFQ).

Review: Strategies for managing sexual dysfunction induced by antidepressant medication

Comparison: 1 Sildenafil vs placebo

Outcome: 14 Endpoint Sexual Function Questionnaire (SFQ)

Study or subgroup	Sildenafil N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Desire						
Nurnberg 2008	49	17.3 (5.1)	49	16.4 (5.2)		0.90 [-1.14, 2.94]
2 Arousal-sensation						
Nurnberg 2008	49	10.3 (4.2)	49	10.4 (4.2)		-0.10 [-1.76, 1.56]
3 Arousal-lubrication						
Nurnberg 2008	49	6.2 (2.2)	49	5.6 (2.3)		0.60 [-0.29, 1.49]
4 Orgasm						
Nurnberg 2008	49	8.6 (3.9)	49	8.6 (3)		0.0 [-1.38, 1.38]
5 Enjoyment						
Nurnberg 2008	49	18 (5.7)	49	16.9 (5.4)		1.10 [-1.10, 3.30]
6 Pain						
Nurnberg 2008	49	14.1 (1.9)	49	13.9 (1.8)		0.20 [-0.53, 0.93]
7 Partner						
Nurnberg 2008	49	8.2 (1.6)	49	7.9 (2)		0.30 [-0.42, 1.02]

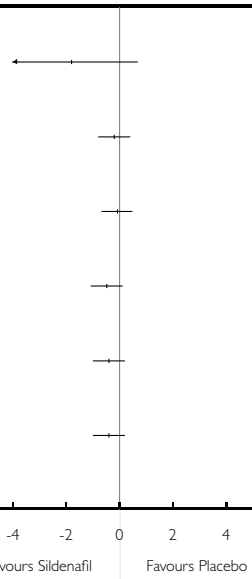
Analysis 1.15. Comparison 1 Sildenafil vs placebo, Outcome 15 UNM Sexual Function Inventory.

Review: Strategies for managing sexual dysfunction induced by antidepressant medication

Comparison: 1 Sildenafil vs placebo

Outcome: 15 UNM Sexual Function Inventory

Study or subgroup	Sildenafil N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Total score						
Nurnberg 2008	49	20.2 (6.4)	49	22 (6.1)		-1.80 [-4.28, 0.68]
2 Desire						
Nurnberg 2008	49	4.1 (1.5)	49	4.3 (1.6)		-0.20 [-0.81, 0.41]
3 Sexual arousal						
Nurnberg 2008	49	4.3 (1.5)	49	4.4 (1.5)		-0.10 [-0.69, 0.49]
4 Lubrication						
Nurnberg 2008	49	3.4 (1.4)	49	3.9 (1.6)		-0.50 [-1.10, 0.10]
5 Ability to reach orgasm						
Nurnberg 2008	49	4.6 (1.6)	49	5 (1.4)		-0.40 [-1.00, 0.20]
6 Overall satisfaction						
Nurnberg 2008	49	4 (1.5)	49	4.4 (1.5)		-0.40 [-0.99, 0.19]



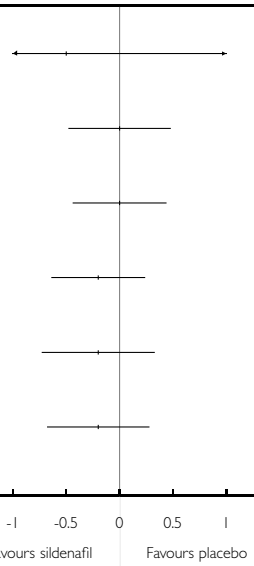
Analysis 1.16. Comparison 1 Sildenafil vs placebo, Outcome 16 Females: endpoint Arizona Sexual Experience Scale scores.

Review: Strategies for managing sexual dysfunction induced by antidepressant medication

Comparison: 1 Sildenafil vs placebo

Outcome: 16 Females: endpoint Arizona Sexual Experience Scale scores

Study or subgroup	Sildenafil N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Total score						
Nurnberg 2008	49	19.5 (4.6)	49	20 (4.2)		-0.50 [-2.24, 1.24]
2 Sexual desire						
Nurnberg 2008	49	4.2 (1.2)	49	4.2 (1.2)		0.0 [-0.48, 0.48]
3 Arousal						
Nurnberg 2008	49	4.1 (1.1)	49	4.1 (1.1)		0.0 [-0.44, 0.44]
4 Orgasm (ability)						
Nurnberg 2008	49	4.3 (1.2)	49	4.5 (1)		-0.20 [-0.64, 0.24]
5 Orgasm (satisfaction)						
Nurnberg 2008	49	3.6 (1.4)	49	3.8 (1.3)		-0.20 [-0.73, 0.33]
6 Lubrication						
Nurnberg 2008	49	3.3 (1.1)	49	3.5 (1.3)		-0.20 [-0.68, 0.28]



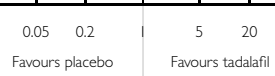
Analysis 2.1. Comparison 2 Tadalafil vs placebo, Outcome 1 Global Assessment Questions.

Review: Strategies for managing sexual dysfunction induced by antidepressant medication

Comparison: 2 Tadalafil vs placebo

Outcome: 1 Global Assessment Questions

Study or subgroup	Tadalafil n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Has the treatment you have been taking improved your erectile function?					
Evliyaoğ lu 2011	23/25	2/25		100.0 %	11.50 [3.03, 43.67]
Subtotal (95% CI)	**25**	**25**		**100.0 %**	**11.50 [3.03, 43.67]**
Total events: 23 (Tadalafil), 2 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.59 (P = 0.00033)					
2 Has the treatment improved your ability to engage in sexual activity?					
Evliyaoğ lu 2011	23/25	2/25		100.0 %	11.50 [3.03, 43.67]
Subtotal (95% CI)	**25**	**25**		**100.0 %**	**11.50 [3.03, 43.67]**
Total events: 23 (Tadalafil), 2 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.59 (P = 0.00033)					
Test for subgroup differences: Chi^2 = 0.0, df = 1 (P = 1.00), I^2 =0.0%					

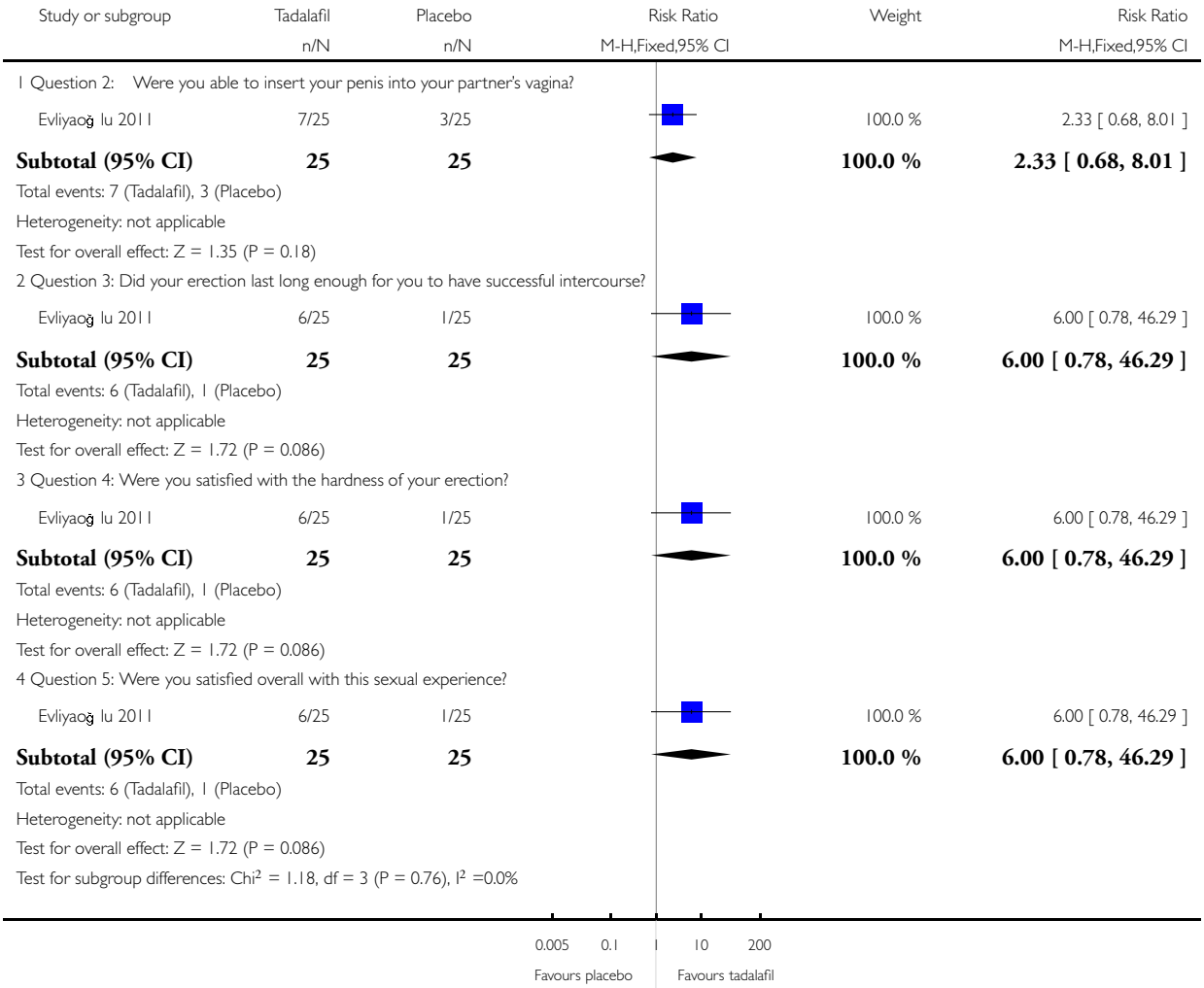


Analysis 2.2. Comparison 2 Tadalafil vs placebo, Outcome 2 Endpoint Sexual Encounter Profile (SEP).

Review: Strategies for managing sexual dysfunction induced by antidepressant medication

Comparison: 2 Tadalafil vs placebo

Outcome: 2 Endpoint Sexual Encounter Profile (SEP)

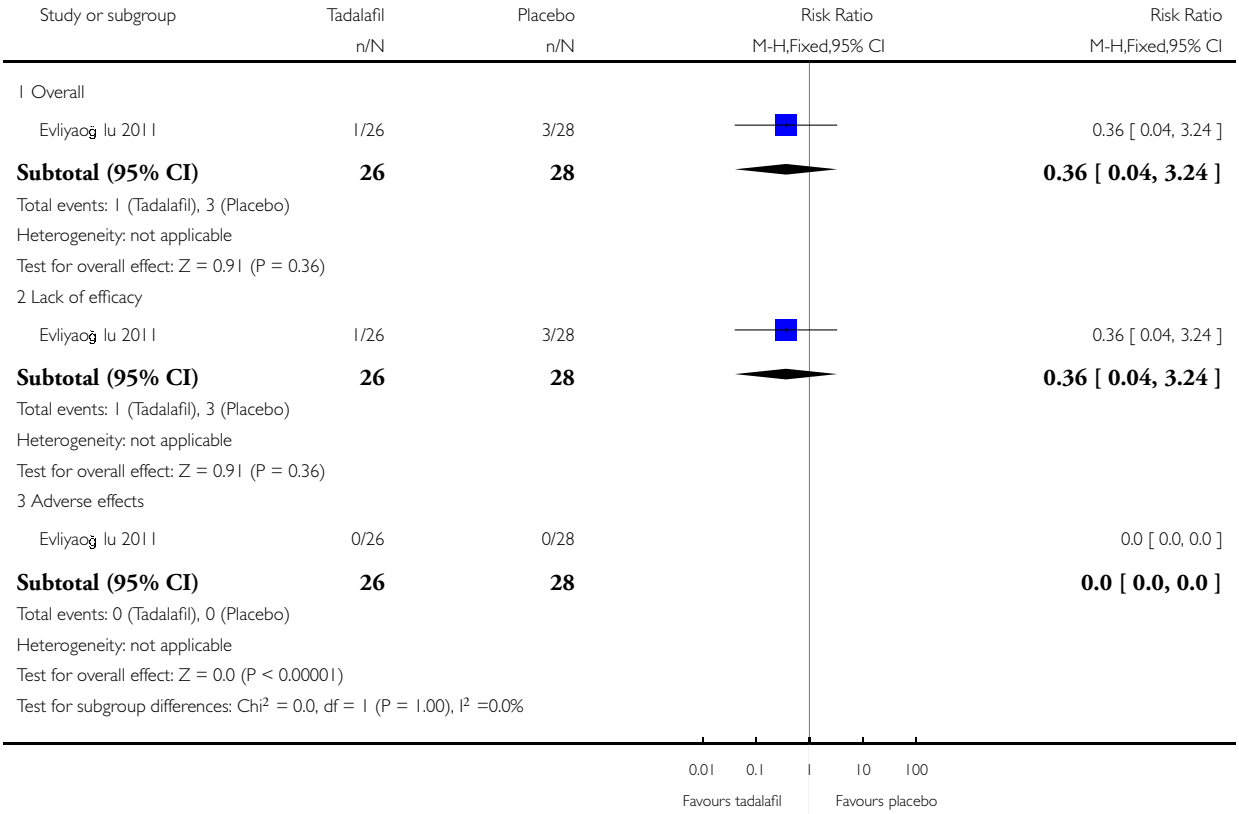


Analysis 2.3. Comparison 2 Tadalafil vs placebo, Outcome 3 Dropouts.

Review: Strategies for managing sexual dysfunction induced by antidepressant medication

Comparison: 2 Tadalafil vs placebo

Outcome: 3 Dropouts



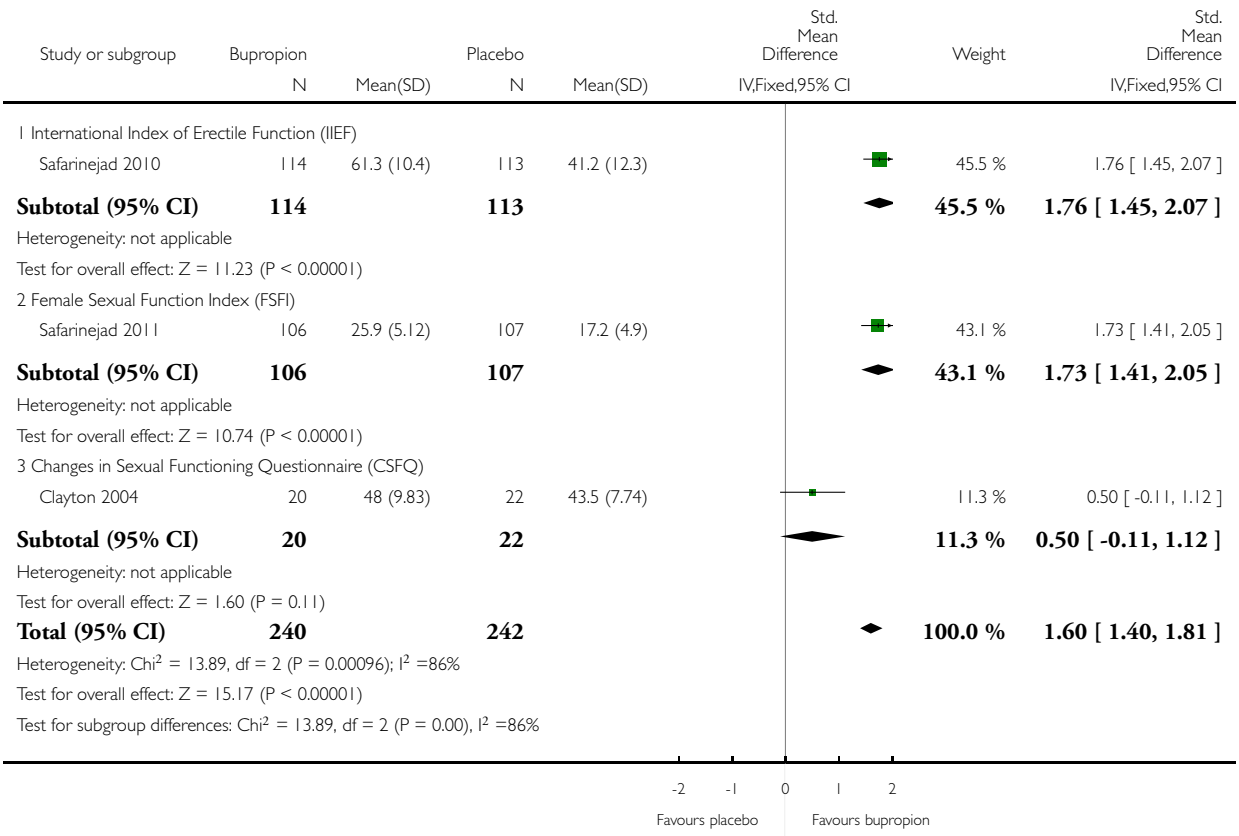
Analysis 3.1. Comparison 3 Bupropion vs placebo, Outcome 1 Endpoint scale total scores.

Review: Strategies for managing sexual dysfunction induced by antidepressant medication

Comparison: 3 Bupropion vs placebo

Outcome: 1 Endpoint scale total scores

Study or subgroup	Bupropion N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
1 International Index of Erectile Function (IIEF)							
Safarinejad 2010	114	61.3 (10.4)	113	41.2 (12.3)		45.5 %	1.76 [1.45, 2.07]
Subtotal (95% CI)	**114**		**113**			**45.5 %**	**1.76 [1.45, 2.07]**
Heterogeneity: not applicable							
Test for overall effect: Z = 11.23 (P < 0.00001)							
2 Female Sexual Function Index (FSFI)							
Safarinejad 2011	106	25.9 (5.12)	107	17.2 (4.9)		43.1 %	1.73 [1.41, 2.05]
Subtotal (95% CI)	**106**		**107**			**43.1 %**	**1.73 [1.41, 2.05]**
Heterogeneity: not applicable							
Test for overall effect: Z = 10.74 (P < 0.00001)							
3 Changes in Sexual Functioning Questionnaire (CSFQ)							
Clayton 2004	20	48 (9.83)	22	43.5 (7.74)		11.3 %	0.50 [-0.11, 1.12]
Subtotal (95% CI)	**20**		**22**			**11.3 %**	**0.50 [-0.11, 1.12]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.60 (P = 0.11)							
Total (95% CI)	**240**		**242**			**100.0 %**	**1.60 [1.40, 1.81]**
Heterogeneity: Chi^2 = 13.89, df = 2 (P = 0.00096); I^2 =86%							
Test for overall effect: Z = 15.17 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 13.89, df = 2 (P = 0.00), I^2 =86%							

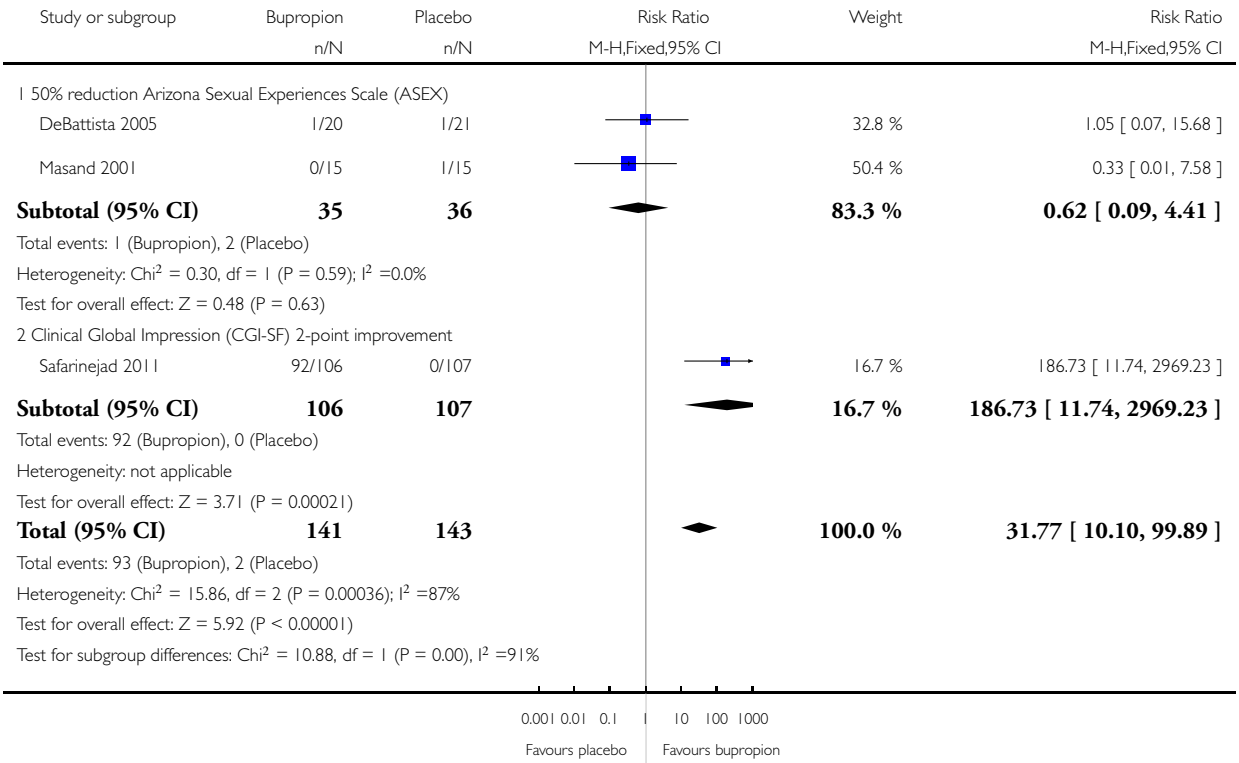


Analysis 3.2. Comparison 3 Bupropion vs placebo, Outcome 2 Response (as defined by study).

Review: Strategies for managing sexual dysfunction induced by antidepressant medication

Comparison: 3 Bupropion vs placebo

Outcome: 2 Response (as defined by study)



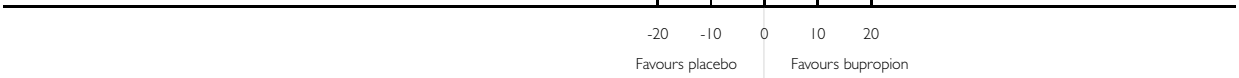
Analysis 3.3. Comparison 3 Bupropion vs placebo, Outcome 3 Endpoint International Index of Erectile Function (IIEF).

Review: Strategies for managing sexual dysfunction induced by antidepressant medication

Comparison: 3 Bupropion vs placebo

Outcome: 3 Endpoint International Index of Erectile Function (IIEF)

Study or subgroup	Bupropion N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Total score							
Safarinejad 2010	114	61.3 (10.4)	113	41.2 (12.3)		100.0 %	20.10 [17.14, 23.06]
Subtotal (95% CI)	**114**		**113**			**100.0 %**	**20.10 [17.14, 23.06]**
Heterogeneity: not applicable							
Test for overall effect: Z = 13.29 (P < 0.00001)							
2 Erectile function							
Safarinejad 2010	114	27.4 (2.8)	113	18.1 (5.4)		100.0 %	9.30 [8.18, 10.42]
Subtotal (95% CI)	**114**		**113**			**100.0 %**	**9.30 [8.18, 10.42]**
Heterogeneity: not applicable							
Test for overall effect: Z = 16.27 (P < 0.00001)							
3 Orgasmic function							
Safarinejad 2010	114	8.3 (2.1)	113	5.6 (2.1)		100.0 %	2.70 [2.15, 3.25]
Subtotal (95% CI)	**114**		**113**			**100.0 %**	**2.70 [2.15, 3.25]**
Heterogeneity: not applicable							
Test for overall effect: Z = 9.69 (P < 0.00001)							
4 Sexual desire							
Safarinejad 2010	114	7.7 (1.4)	113	5.6 (1.2)		100.0 %	2.10 [1.76, 2.44]
Subtotal (95% CI)	**114**		**113**			**100.0 %**	**2.10 [1.76, 2.44]**
Heterogeneity: not applicable							
Test for overall effect: Z = 12.14 (P < 0.00001)							
5 Intercourse satisfaction							
Safarinejad 2010	114	10.3 (2.4)	113	6.7 (2.2)		100.0 %	3.60 [3.00, 4.20]
Subtotal (95% CI)	**114**		**113**			**100.0 %**	**3.60 [3.00, 4.20]**
Heterogeneity: not applicable							
Test for overall effect: Z = 11.78 (P < 0.00001)							
6 Overall satisfaction							
Safarinejad 2010	114	7.6 (2.4)	113	5 (2.3)		100.0 %	2.60 [1.99, 3.21]
Subtotal (95% CI)	**114**		**113**			**100.0 %**	**2.60 [1.99, 3.21]**
Heterogeneity: not applicable							
Test for overall effect: Z = 8.33 (P < 0.00001)							



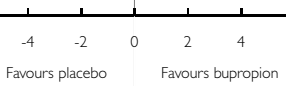
Analysis 3.4. Comparison 3 Bupropion vs placebo, Outcome 4 Endpoint Female Sexual Function Index score.

Review: Strategies for managing sexual dysfunction induced by antidepressant medication

Comparison: 3 Bupropion vs placebo

Outcome: 4 Endpoint Female Sexual Function Index score

Study or subgroup	Bupropion N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Total score						
Safarinejad 2011	106	25.9 (5.12)	107	17.2 (4.9)		8.70 [7.35, 10.05]
2 Desire						
Safarinejad 2011	106	4.1 (0.7)	107	2.2 (0.4)		1.90 [1.75, 2.05]
3 Arousal						
Safarinejad 2011	106	4.4 (0.6)	107	3.1 (0.4)		1.30 [1.16, 1.44]
4 Lubrication						
Safarinejad 2011	106	4.4 (0.4)	107	2.5 (0.3)		1.90 [1.80, 2.00]
5 Orgasm						
Safarinejad 2011	106	4.4 (0.5)	107	2.5 (0.4)		1.90 [1.78, 2.02]
6 Satisfaction						
Safarinejad 2011	106	4.2 (0.7)	107	2.6 (0.3)		1.60 [1.46, 1.74]
7 Pain						
Safarinejad 2011	106	4.4 (0.4)	107	4.3 (0.4)		0.10 [-0.01, 0.21]



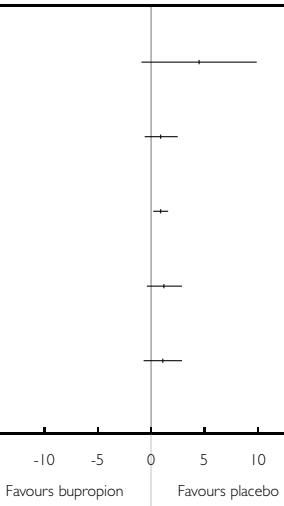
Analysis 3.5. Comparison 3 Bupropion vs placebo, Outcome 5 Endpoint Changes in Sexual Functioning Questionnaire score.

Review: Strategies for managing sexual dysfunction induced by antidepressant medication

Comparison: 3 Bupropion vs placebo

Outcome: 5 Endpoint Changes in Sexual Functioning Questionnaire score

Study or subgroup	Bupropion N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Total score						
Clayton 2004	20	48 (9.83)	22	43.5 (7.74)		4.50 [-0.89, 9.89]
2 Desire/interest						
Clayton 2004	20	8.85 (2.7)	22	7.91 (2.33)		0.94 [-0.59, 2.47]
3 Desire/frequency						
Clayton 2004	20	6.65 (1.05)	22	5.77 (1.15)		0.88 [0.21, 1.55]
4 Arousal/excitement						
Clayton 2004	20	10.5 (2.8)	22	9.27 (2.55)		1.23 [-0.40, 2.86]
5 Completion/orgasm						
Clayton 2004	20	10.05 (2.8)	22	8.91 (3.16)		1.14 [-0.66, 2.94]



Analysis 3.6. Comparison 3 Bupropion vs placebo, Outcome 6 Dropouts.

Review: Strategies for managing sexual dysfunction induced by antidepressant medication

Comparison: 3 Bupropion vs placebo

Outcome: 6 Dropouts

Study or subgroup	Bupropion n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Clayton 2004	9/29	4/26		2.02 [0.70, 5.78]
DeBattista 2005	0/20	0/21		0.0 [0.0, 0.0]
Masand 2001	1/16	0/15		2.82 [0.12, 64.39]
Safarinejad 2010	13/117	15/117		0.87 [0.43, 1.74]
Safarinejad 2011	9/109	10/109		0.90 [0.38, 2.13]
Total (95% CI)	**291**	**288**		**1.08 [0.67, 1.72]**

Total events: 32 (Bupropion), 29 (Placebo)

Heterogeneity: $Chi^2 = 2.27$, df = 3 (P = 0.52); $I^2 = 0.0\%$

Test for overall effect: Z = 0.30 (P = 0.76)

Test for subgroup differences: Not applicable

Analysis 3.7. Comparison 3 Bupropion vs placebo, Outcome 7 Endpoint Hamilton Rating Scale for Depression score.

Review: Strategies for managing sexual dysfunction induced by antidepressant medication

Comparison: 3 Bupropion vs placebo

Outcome: 7 Endpoint Hamilton Rating Scale for Depression score

Study or subgroup	Bupropion N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Clayton 2004	20	4.05 (3.49)	22	4.65 (3.16)		-0.60 [-2.62, 1.42]

Analysis 3.8. Comparison 3 Bupropion vs placebo, Outcome 8 Endpoint Clinical Global Impression (CGI - SF).

Review: Strategies for managing sexual dysfunction induced by antidepressant medication

Comparison: 3 Bupropion vs placebo

Outcome: 8 Endpoint Clinical Global Impression (CGI - SF)

Study or subgroup	Bupropion N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Male							
Safarinejad 2010	114	2.4 (1.2)	113	3.9 (1.1)		19.7 %	-1.50 [-1.80, -1.20]
Subtotal (95% CI)	**114**		**113**			**19.7 %**	**-1.50 [-1.80, -1.20]**
Heterogeneity: not applicable							
Test for overall effect: Z = 9.82 (P < 0.00001)							
2 Female							
Safarinejad 2011	106	2.4 (0.6)	107	4.2 (0.5)		80.3 %	-1.80 [-1.95, -1.65]
Subtotal (95% CI)	**106**		**107**			**80.3 %**	**-1.80 [-1.95, -1.65]**
Heterogeneity: not applicable							
Test for overall effect: Z = 23.77 (P < 0.00001)							
Total (95% CI)	**220**		**220**			**100.0 %**	**-1.74 [-1.87, -1.61]**
Heterogeneity: Chi^2 = 3.10, df = 1 (P = 0.08); I^2 =68%							
Test for overall effect: Z = 25.66 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 3.10, df = 1 (P = 0.08), I^2 =68%							

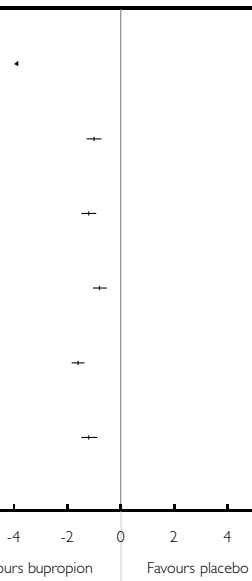
Analysis 3.9. Comparison 3 Bupropion vs placebo, Outcome 9 Endpoint ASEX.

Review: Strategies for managing sexual dysfunction induced by antidepressant medication

Comparison: 3 Bupropion vs placebo

Outcome: 9 Endpoint ASEX

Study or subgroup	Bupropion N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Total score						
Safarinejad 2010	114	15.5 (4.3)	113	21.5 (4.7)		-6.00 [-7.17, -4.83]
2 Erectile function						
Safarinejad 2010	114	3.2 (1)	113	4.2 (1.2)		-1.00 [-1.29, -0.71]
3 Sexual desire						
Safarinejad 2010	114	3.1 (1.1)	113	4.3 (1.1)		-1.20 [-1.49, -0.91]
4 Arousal						
Safarinejad 2010	114	3.2 (1)	113	4 (1)		-0.80 [-1.06, -0.54]
5 Ability to reach orgasm						
Safarinejad 2010	114	3 (0.9)	113	4.6 (1)		-1.60 [-1.85, -1.35]
6 Satisfaction with orgasm						
Safarinejad 2010	114	3.1 (1.1)	113	4.3 (1.2)		-1.20 [-1.50, -0.90]



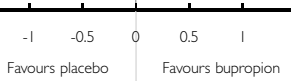
Analysis 3.10. Comparison 3 Bupropion vs placebo, Outcome 10 Endpoint EDITS (participant).

Review: Strategies for managing sexual dysfunction induced by antidepressant medication

Comparison: 3 Bupropion vs placebo

Outcome: 10 Endpoint EDITS (participant)

Study or subgroup	Bupropion N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Total score						
Safarinejad 2010	114	67.4 (10.2)	113	36.3 (11.7)		31.10 [28.24, 33.96]
2 Overall satisfaction						
Safarinejad 2010	114	2.6 (0.14)	113	0.9 (0.22)		1.70 [1.65, 1.75]
3 Expectations						
Safarinejad 2010	114	2.2 (0.12)	113	1.1 (0.16)		1.10 [1.06, 1.14]
4 Likelihood of continuing						
Safarinejad 2010	114	2.6 (0.15)	113	0.9 (0.26)		1.70 [1.64, 1.76]
5 Confidence						
Safarinejad 2010	114	2.7 (0.12)	113	1.3 (0.19)		1.40 [1.36, 1.44]
6 Partner satisfaction						
Safarinejad 2010	114	2.5 (0.16)	113	1 (0.18)		1.50 [1.46, 1.54]
7 Partner desire to continue treatment						
Safarinejad 2010	114	2.7 (0.14)	113	1.2 (0.18)		1.50 [1.46, 1.54]
8 Naturalness of achieving erection						
Safarinejad 2010	114	3.2 (0.11)	113	2.2 (0.2)		1.00 [0.96, 1.04]
9 Naturalness of erection hardness						
Safarinejad 2010	114	2.6 (0.14)	113	1.8 (0.19)		0.80 [0.76, 0.84]
10 Quickness of achieving erection						
Safarinejad 2010	114	2.8 (0.12)	113	1.4 (0.12)		1.40 [1.37, 1.43]
11 Duration that erection lasts						
Safarinejad 2010	114	2.7 (0.14)	113	1.2 (0.22)		1.50 [1.45, 1.55]
12 Ease of use						
Safarinejad 2010	114	3.8 (0.06)	113	3.8 (0.07)		0.0 [-0.02, 0.02]



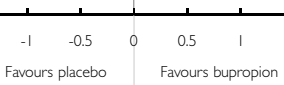
Analysis 3.11. Comparison 3 Bupropion vs placebo, Outcome 11 Endpoint EDITS (partner).

Review: Strategies for managing sexual dysfunction induced by antidepressant medication

Comparison: 3 Bupropion vs placebo

Outcome: 11 Endpoint EDITS (partner)

Study or subgroup	Bupropion N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Total score						
Safarinejad 2010	114	64.1 (3.2)	113	36.1 (3.42)		28.00 [27.14, 28.86]
2 Overall satisfaction						
Safarinejad 2010	114	2.4 (0.12)	113	1 (0.18)		1.40 [1.36, 1.44]
3 Expectations						
Safarinejad 2010	114	2.2 (0.15)	113	0.8 (0.24)		1.40 [1.35, 1.45]
4 Sexual desirability						
Safarinejad 2010	114	2.4 (0.1)	113	2.1 (0.13)		0.30 [0.27, 0.33]
5 Participant's feelings about continuing treatment						
Safarinejad 2010	114	2.7 (0.16)	113	1.2 (0.23)		1.50 [1.45, 1.55]
6 Duration that erection lasts						
Safarinejad 2010	114	2.5 (0.15)	113	1.2 (0.22)		1.30 [1.25, 1.35]



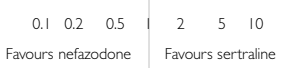
Analysis 4.1. Comparison 4 Nefazodone vs sertraline, Outcome 1 Re-emergence of antidepressant-induced sexual dysfunction (physician rated).

Review: Strategies for managing sexual dysfunction induced by antidepressant medication

Comparison: 4 Nefazodone vs sertraline

Outcome: 1 Re-emergence of antidepressant-induced sexual dysfunction (physician rated)

Study or subgroup	Nefazodone n/N	Sertraline n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Week 1				
Ferguson 2001	7/39	18/33		0.33 [0.16, 0.69]
2 Endpoint				
Ferguson 2001	10/39	25/33		0.34 [0.19, 0.60]



Analysis 4.2. Comparison 4 Nefazodone vs sertraline, Outcome 2 Overall degree of sexual satisfaction (participant rated).

Review: Strategies for managing sexual dysfunction induced by antidepressant medication

Comparison: 4 Nefazodone vs sertraline

Outcome: 2 Overall degree of sexual satisfaction (participant rated)

Study or subgroup	Nefazodone N	Mean(SD)	Sertraline N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Baseline						
Ferguson 2001	39	71.2 (26.97)	27	65.95 (24.4)		5.25 [-7.25, 17.75]
2 Week 8						
Ferguson 2001	28	62.39 (37.85)	16	45.17 (34.05)		17.22 [-4.57, 39.01]
3 Last rating recorded						
Ferguson 2001	38	62.41 (37.89)	26	41.52 (33.84)		20.89 [3.16, 38.62]

Analysis 4.3. Comparison 4 Nefazodone vs sertraline, Outcome 3 Dropouts.

Review: Strategies for managing sexual dysfunction induced by antidepressant medication

Comparison: 4 Nefazodone vs sertraline

Outcome: 3 Dropouts

Study or subgroup	Nefazodone n/N	Sertraline n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Overall				
Ferguson 2001	12/41	12/34		0.83 [0.43, 1.60]
2 Attributed to adverse effects				
Ferguson 2001	5/41	9/34		0.46 [0.17, 1.25]

Analysis 4.4. Comparison 4 Nefazodone vs sertraline, Outcome 4 Hamilton Rating Scale for Depression score.

Review: Strategies for managing sexual dysfunction induced by antidepressant medication

Comparison: 4 Nefazodone vs sertraline

Outcome: 4 Hamilton Rating Scale for Depression score

Study or subgroup	Nefazodone N	Mean(SD)	Sertraline N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Baseline						
Ferguson 2001	42	11.54 (6.85)	30	10.62 (5.9)		0.92 [-2.04, 3.88]
2 Week 8						
Ferguson 2001	42	6.88 (6.81)	30	8.45 (5.86)		-1.57 [-4.51, 1.37]

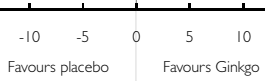
Analysis 5.1. Comparison 5 Ginkgo biloba vs placebo, Outcome 1 Endpoint sexual function ratings (investigator questionnaire).

Review: Strategies for managing sexual dysfunction induced by antidepressant medication

Comparison: 5 Ginkgo biloba vs placebo

Outcome: 1 Endpoint sexual function ratings (investigator questionnaire)

Study or subgroup	Ginkgo biloba N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Sexual desire						
Kang 2002	12	2.91 (1.31)	13	2.76 (1.58)		0.15 [-0.98, 1.28]
2 Overall sexual function						
Kang 2002	12	2.75 (1.28)	13	3.23 (1.23)		-0.48 [-1.47, 0.51]
3 Erection maintenance time						
Kang 2002	12	3.6 (1.17)	13	3.5 (0.97)		0.10 [-0.75, 0.95]
4 Orgasm frequency						
Kang 2002	12	2.54 (1.5)	13	2 (1.35)		0.54 [-0.58, 1.66]
5 Satisfaction to orgasm						
Kang 2002	12	2.72 (1.1)	13	3.84 (1.14)		-1.12 [-2.00, -0.24]



Analysis 5.2. Comparison 5 Ginkgo biloba vs placebo, Outcome 2 Sexual Dysfunction Scale (investigator developed).

Review: Strategies for managing sexual dysfunction induced by antidepressant medication

Comparison: 5 Ginkgo biloba vs placebo

Outcome: 2 Sexual Dysfunction Scale (investigator developed)

Study or subgroup	Ginkgo biloba N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Baseline						
Wheatley 2004	11	14.4 (3.08)	13	12.6 (4.11)		1.80 [-1.08, 4.68]
2 Week 12						
Wheatley 2004	11	10.9 (7.69)	13	7.1 (6.45)		3.80 [-1.94, 9.54]

Analysis 5.3. Comparison 5 Ginkgo biloba vs placebo, Outcome 3 Dropouts.

Review: Strategies for managing sexual dysfunction induced by antidepressant medication

Comparison: 5 Ginkgo biloba vs placebo

Outcome: 3 Dropouts

Study or subgroup	Ginkgo biloba n/N	placebo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Kang 2002	7/19	5/18		1.33 [0.51, 3.43]

Analysis 6.1. Comparison 6 Granisetron vs placebo, Outcome 1 Change from baseline on Sexual Side Effects Scale (SSES) total score.

Review: Strategies for managing sexual dysfunction induced by antidepressant medication

Comparison: 6 Granisetron vs placebo

Outcome: 1 Change from baseline on Sexual Side Effects Scale (SSES) total score

Study or subgroup	Granisetron N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Nelson 2001	20	2.8 (3.1)	20	2.7 (4.3)		0.10 [-2.22, 2.42]

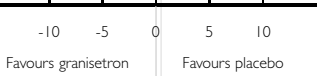
Analysis 6.2. Comparison 6 Granisetron vs placebo, Outcome 2 Endpoint Feiger Sexual Function and Satisfaction Questionnaire score.

Review: Strategies for managing sexual dysfunction induced by antidepressant medication

Comparison: 6 Granisetron vs placebo

Outcome: 2 Endpoint Feiger Sexual Function and Satisfaction Questionnaire score

Study or subgroup	Granisetron N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Total score						
Jespersen 2004	5	18 (6.8)	7	16.4 (5.1)		1.60 [-5.46, 8.66]
2 Item 1						
Jespersen 2004	5	3.3 (1)	7	1.9 (0.7)		1.40 [0.38, 2.42]
3 Item 2						
Jespersen 2004	5	4.3 (1)	7	3.1 (1.1)		1.20 [0.00, 2.40]
4 Item 3						
Jespersen 2004	5	2.3 (1.9)	7	3.4 (1.7)		-1.10 [-3.19, 0.99]
5 Item 4						
Jespersen 2004	5	2.3 (1.9)	7	2.6 (1.7)		-0.30 [-2.39, 1.79]



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Study or subgroup	Granisetron N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
6 Item 5						
Jespersen 2004	5	3 (1.2)	7	2.7 (1.3)		0.30 [-1.13, 1.73]
7 Item 6						
Jespersen 2004	5	3 (1.2)	7	2.7 (1.3)		0.30 [-1.13, 1.73]

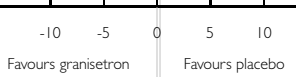
Analysis 6.3. Comparison 6 Granisetron vs placebo, Outcome 3 Endpoint Arizona Sexual Experience Scale (ASEX) score.

Review: Strategies for managing sexual dysfunction induced by antidepressant medication

Comparison: 6 Granisetron vs placebo

Outcome: 3 Endpoint Arizona Sexual Experience Scale (ASEX) score

Study or subgroup	Granisetron N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Total score						
Jespersen 2004	5	20.3 (9.7)	7	12.4 (6.5)		7.90 [-1.87, 17.67]
2 Sexual desire						
Jespersen 2004	5	4.3 (2.4)	7	2.9 (1.7)		1.40 [-1.05, 3.85]
3 Arousal						
Jespersen 2004	5	4.3 (2.4)	7	2.9 (1.7)		1.40 [-1.05, 3.85]
4 Lubrication						
Jespersen 2004	5	3.8 (2.6)	7	3.4 (1.9)		0.40 [-2.28, 3.08]
5 Orgasm (ability)						
Jespersen 2004	5	4.3 (2.1)	7	3.6 (1.3)		0.70 [-1.38, 2.78]
6 Orgasm (satisfaction)						
Jespersen 2004	5	3.8 (0.5)	7	2.8 (0.8)		1.00 [0.26, 1.74]

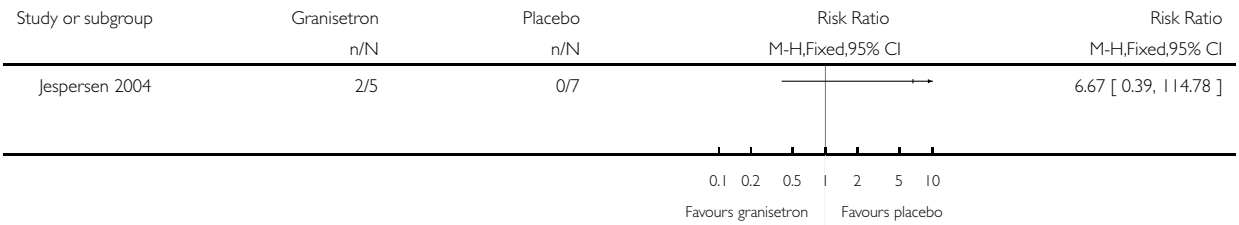


Analysis 6.4. Comparison 6 Granisetron vs placebo, Outcome 4 Dropouts.

Review: Strategies for managing sexual dysfunction induced by antidepressant medication

Comparison: 6 Granisetron vs placebo

Outcome: 4 Dropouts

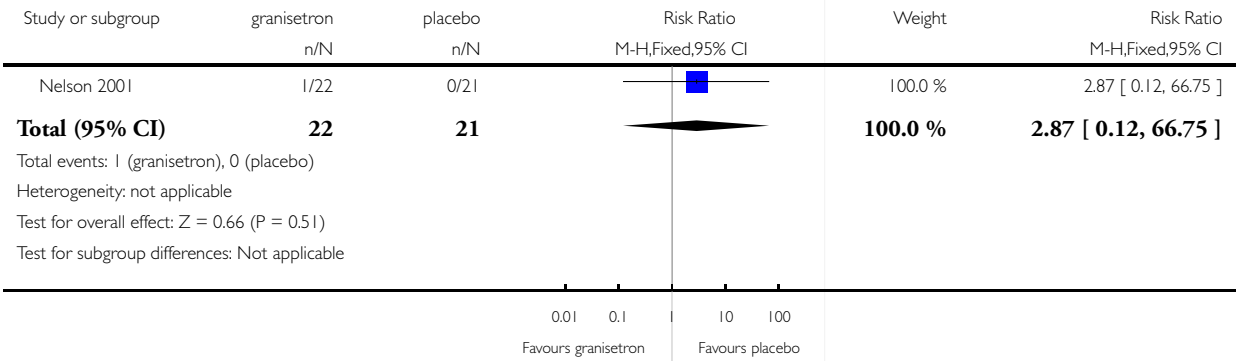


Analysis 6.5. Comparison 6 Granisetron vs placebo, Outcome 5 Recurrence of mood symptoms.

Review: Strategies for managing sexual dysfunction induced by antidepressant medication

Comparison: 6 Granisetron vs placebo

Outcome: 5 Recurrence of mood symptoms



Analysis 7.1. Comparison 7 VML-670 vs placebo, Outcome 1 Absence of sexual dysfunction at end point.

Review: Strategies for managing sexual dysfunction induced by antidepressant medication

Comparison: 7 VML-670 vs placebo

Outcome: 1 Absence of sexual dysfunction at end point

Study or subgroup	VML-670 n/N	placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Baldwin 2008	48/138	36/128		100.0 %	1.24 [0.86, 1.77]
Total (95% CI)	**138**	**128**		**100.0 %**	**1.24 [0.86, 1.77]**

Total events: 48 (VML-670), 36 (placebo)
Heterogeneity: not applicable
Test for overall effect: Z = 1.16 (P = 0.25)
Test for subgroup differences: Not applicable

Analysis 7.2. Comparison 7 VML-670 vs placebo, Outcome 2 'Improved' or 'much improved' on Clinical Global Impression.

Review: Strategies for managing sexual dysfunction induced by antidepressant medication

Comparison: 7 VML-670 vs placebo

Outcome: 2 'Improved' or 'much improved' on Clinical Global Impression

Study or subgroup	VML-670 n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Baldwin 2008	24/138	18/128		100.0 %	1.24 [0.71, 2.17]
Total (95% CI)	**138**	**128**		**100.0 %**	**1.24 [0.71, 2.17]**

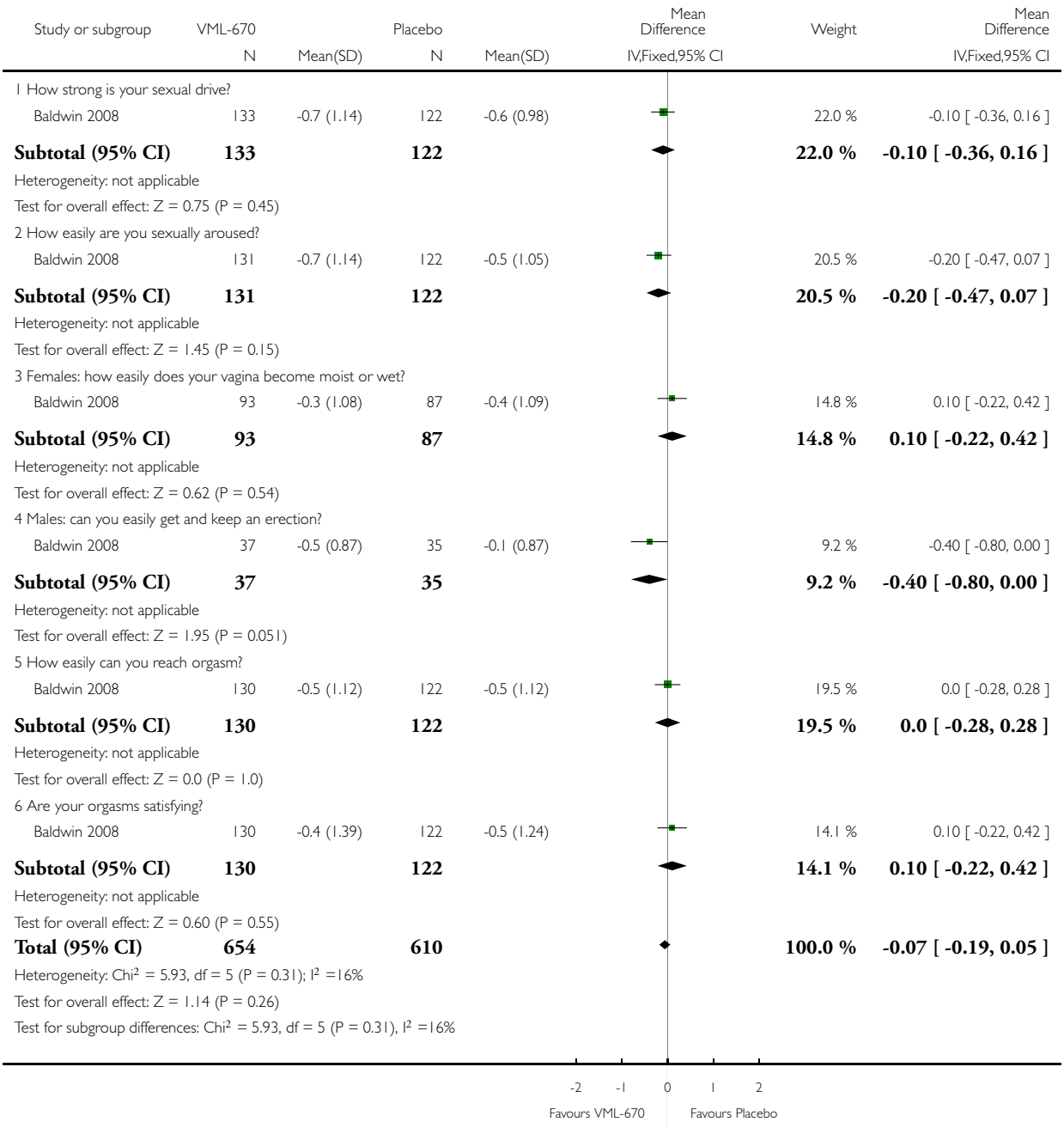
Total events: 24 (VML-670), 18 (Placebo)
Heterogeneity: not applicable
Test for overall effect: Z = 0.74 (P = 0.46)
Test for subgroup differences: Not applicable

Analysis 7.3. Comparison 7 VML-670 vs placebo, Outcome 3 Change in Arizona Sexual Experiences Scale (ASEX) item scores.

Review: Strategies for managing sexual dysfunction induced by antidepressant medication

Comparison: 7 VML-670 vs placebo

Outcome: 3 Change in Arizona Sexual Experiences Scale (ASEX) item scores

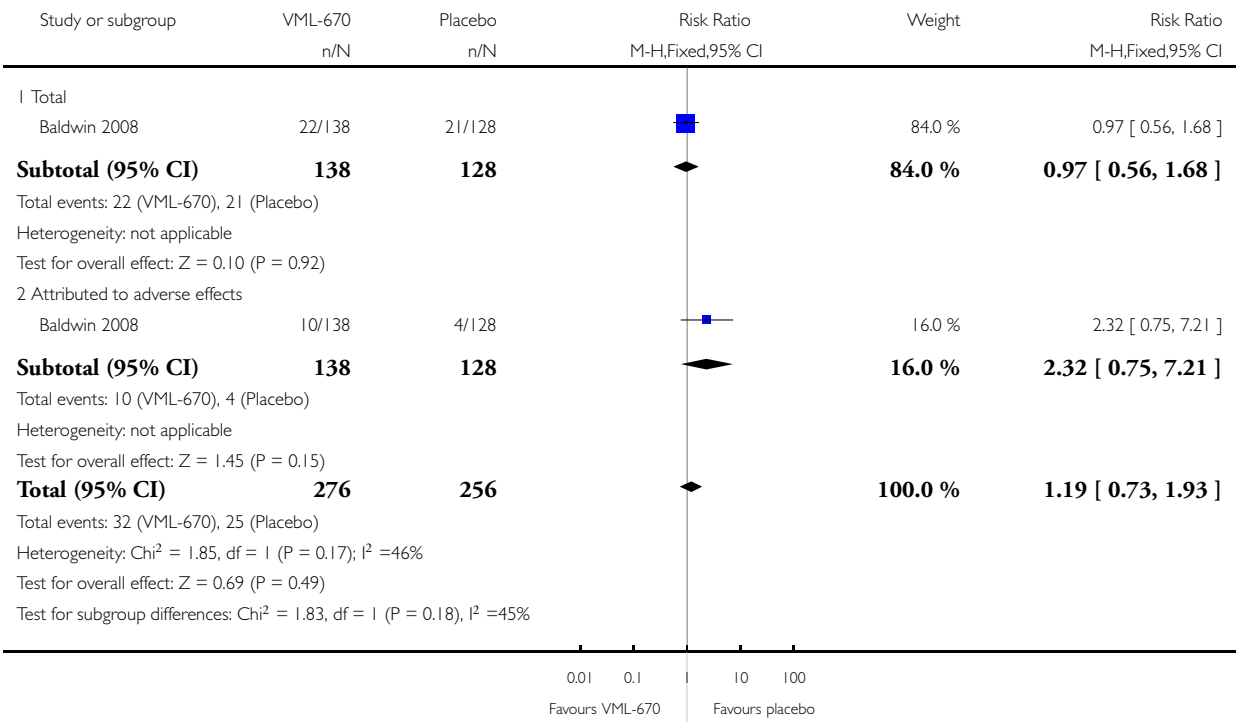


Analysis 7.4. Comparison 7 VML-670 vs placebo, Outcome 4 Dropouts.

Review: Strategies for managing sexual dysfunction induced by antidepressant medication

Comparison: 7 VML-670 vs placebo

Outcome: 4 Dropouts



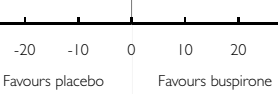
Analysis 8.1. Comparison 8 Buspirone vs placebo, Outcome 1 Change in patient-rated visual analogue scales.

Review: Strategies for managing sexual dysfunction induced by antidepressant medication

Comparison: 8 Buspirone vs placebo

Outcome: 1 Change in patient-rated visual analogue scales

Study or subgroup	Buspirone N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Overall function (total of interest, lubrication, orgasm, pleasure)							
Michelson 2000	19	40.8 (64.2)	20	37.7 (67.8)		100.0 %	3.10 [-38.33, 44.53]
Subtotal (95% CI)	**19**		**20**			**100.0 %**	**3.10 [-38.33, 44.53]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.15 (P = 0.88)							
2 Mood							
Michelson 2000	19	1.4 (15.2)	20	0.6 (11.2)		100.0 %	0.80 [-7.61, 9.21]
Subtotal (95% CI)	**19**		**20**			**100.0 %**	**0.80 [-7.61, 9.21]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.19 (P = 0.85)							
3 Energy							
Michelson 2000	19	2.1 (15.1)	20	-3.2 (14.1)		100.0 %	5.30 [-3.88, 14.48]
Subtotal (95% CI)	**19**		**20**			**100.0 %**	**5.30 [-3.88, 14.48]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.13 (P = 0.26)							
4 Interest/desire							
Michelson 2000	19	12.9 (17.5)	20	10.2 (16.5)		100.0 %	2.70 [-7.99, 13.39]
Subtotal (95% CI)	**19**		**20**			**100.0 %**	**2.70 [-7.99, 13.39]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.50 (P = 0.62)							
5 Lubrication							
Michelson 2000	19	13.6 (19.1)	20	3.7 (23.9)		100.0 %	9.90 [-3.65, 23.45]
Subtotal (95% CI)	**19**		**20**			**100.0 %**	**9.90 [-3.65, 23.45]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.43 (P = 0.15)							
6 Orgasm							
Michelson 2000	19	7.8 (21.5)	20	14.1 (22.1)		100.0 %	-6.30 [-19.98, 7.38]
Subtotal (95% CI)	**19**		**20**			**100.0 %**	**-6.30 [-19.98, 7.38]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.90 (P = 0.37)							
7 Pleasure							
Michelson 2000	19	6.5 (17.2)	20	9.7 (21.9)		100.0 %	-3.20 [-15.53, 9.13]



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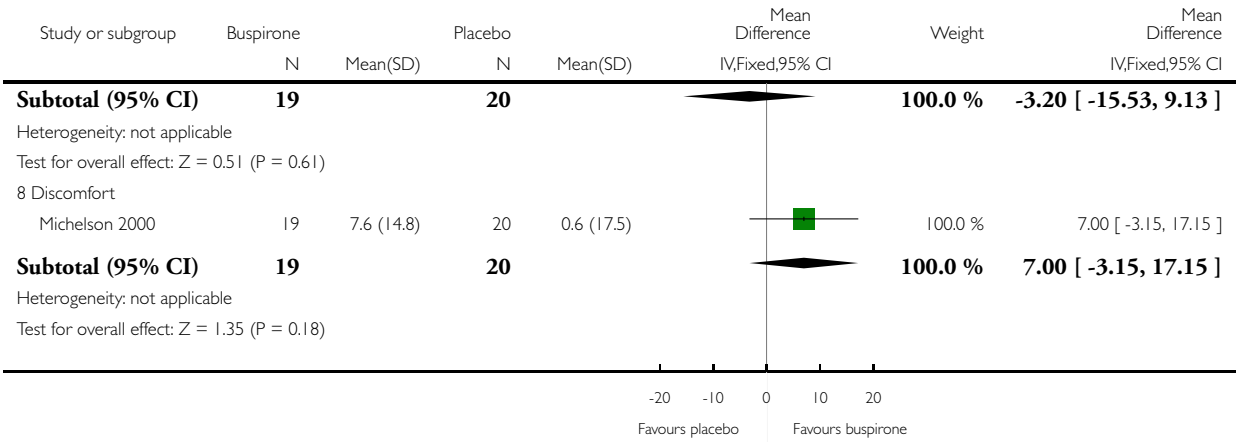
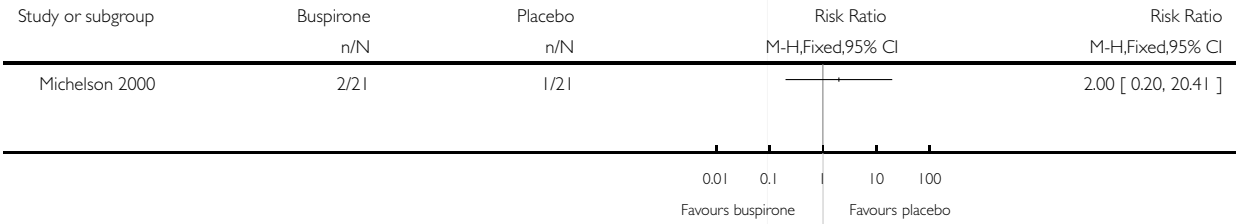


Analysis 8.2. Comparison 8 Buspirone vs placebo, Outcome 2 Dropouts.

Review: Strategies for managing sexual dysfunction induced by antidepressant medication

Comparison: 8 Buspirone vs placebo

Outcome: 2 Dropouts



Analysis 9.1. Comparison 9 Bethanecol vs placebo, Outcome 1 Visual analogue scale of orgasmic function - best score achieved.

Review: Strategies for managing sexual dysfunction induced by antidepressant medication

Comparison: 9 Bethanecol vs placebo

Outcome: 1 Visual analogue scale of orgasmic function - best score achieved

Study or subgroup	Bethanecol N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Bernik 2004	10	5.8 (2.7)	10	2.4 (2.8)		3.40 [0.99, 5.81]

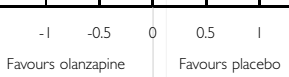
Analysis 10.1. Comparison 10 Olanzapine vs placebo, Outcome 1 Change in patient rated assessment of sexual function.

Review: Strategies for managing sexual dysfunction induced by antidepressant medication

Comparison: 10 Olanzapine vs placebo

Outcome: 1 Change in patient rated assessment of sexual function

Study or subgroup	Olanzapine N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Overall satisfaction						
Michelson 2002	35	-1.5 (1.1)	37	-0.8 (0.9)		-0.70 [-1.17, -0.23]
2 Sexual interest						
Michelson 2002	35	-0.6 (1.1)	37	-0.7 (1)		0.10 [-0.39, 0.59]
3 Psychological arousal						
Michelson 2002	35	-1.1 (1.2)	37	-0.8 (1.2)		-0.30 [-0.85, 0.25]
4 Lubrication						
Michelson 2002	35	-0.9 (1.2)	37	-0.5 (1.1)		-0.40 [-0.93, 0.13]
5 Orgasm						
Michelson 2002	35	-1.1 (1.4)	37	-0.7 (1.1)		-0.40 [-0.98, 0.18]



Analysis 10.2. Comparison 10 Olanzapine vs placebo, Outcome 2 Change in diary ratings (visual analogue scales).

Review: Strategies for managing sexual dysfunction induced by antidepressant medication

Comparison: 10 Olanzapine vs placebo

Outcome: 2 Change in diary ratings (visual analogue scales)

Study or subgroup	Olanzapine N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Overall sexual function						
Michelson 2002	35	6.1 (11.3)	37	5.2 (10.1)		0.90 [-4.06, 5.86]
2 Mood						
Michelson 2002	35	0.3 (1.1)	37	0.2 (1.1)		0.10 [-0.41, 0.61]
3 Energy						
Michelson 2002	35	0 (1.6)	37	0.3 (1.3)		-0.30 [-0.98, 0.38]
4 Sexual interest						
Michelson 2002	35	0.3 (1.8)	37	0.4 (1.3)		-0.10 [-0.83, 0.63]
5 Psychological arousal						
Michelson 2002	35	0.8 (2.2)	37	0.9 (2.5)		-0.10 [-1.19, 0.99]
6 Physical arousal						
Michelson 2002	35	1.4 (2.6)	37	0.8 (2.1)		0.60 [-0.50, 1.70]
7 Orgasm						
Michelson 2002	35	1.6 (2.3)	37	1.2 (2)		0.40 [-0.60, 1.40]
8 Pleasure/enjoyment						
Michelson 2002	35	1.3 (2.6)	37	1 (2.2)		0.30 [-0.82, 1.42]
9 Discomfort						
Michelson 2002	35	0.5 (2.2)	37	0.7 (2)		-0.20 [-1.17, 0.77]

Analysis 10.3. Comparison 10 Olanzapine vs placebo, Outcome 3 Dropouts due to adverse effects.

Review: Strategies for managing sexual dysfunction induced by antidepressant medication

Comparison: 10 Olanzapine vs placebo

Outcome: 3 Dropouts due to adverse effects

Study or subgroup	Olanzapine n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Michelson 2002	7/38	2/39		3.59 [0.80, 16.21]

Analysis 11.1. Comparison 11 Mirtazapine vs placebo, Outcome 1 Change in patient rated assessment of sexual function.

Review: Strategies for managing sexual dysfunction induced by antidepressant medication

Comparison: 11 Mirtazapine vs placebo

Outcome: 1 Change in patient rated assessment of sexual function

Study or subgroup	Mirtazapine N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Overall satisfaction						
Michelson 2002	35	-0.7 (0.8)	37	-0.8 (0.9)		0.10 [-0.29, 0.49]
2 Sexual interest						
Michelson 2002	35	-0.5 (0.8)	37	-0.7 (1)		0.20 [-0.22, 0.62]
3 Psychological arousal						
Michelson 2002	35	-0.6 (0.9)	37	-0.8 (1.2)		0.20 [-0.29, 0.69]
4 Lubrication						
Michelson 2002	35	-0.7 (1.3)	37	-0.5 (1.1)		-0.20 [-0.76, 0.36]
5 Orgasm						
Michelson 2002	35	-0.5 (1.1)	37	-0.7 (1.1)		0.20 [-0.31, 0.71]

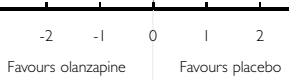
Analysis 11.2. Comparison 11 Mirtazapine vs placebo, Outcome 2 Change in diary ratings (visual analogue scales).

Review: Strategies for managing sexual dysfunction induced by antidepressant medication

Comparison: 11 Mirtazapine vs placebo

Outcome: 2 Change in diary ratings (visual analogue scales)

Study or subgroup	Mirtazapine N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Overall sexual function						
Michelson 2002	35	3.9 (9)	37	5.2 (10.1)		-1.30 [-5.71, 3.11]
2 Mood						
Michelson 2002	35	-0.2 (1.2)	37	0.2 (1.1)		-0.40 [-0.93, 0.13]
3 Energy						
Michelson 2002	35	-0.4 (1.6)	37	0.3 (1.3)		-0.70 [-1.38, -0.02]
4 Sexual interest						
Michelson 2002	35	0.2 (1.3)	37	0.4 (1.3)		-0.20 [-0.80, 0.40]
5 Psychological arousal						
Michelson 2002	35	0.5 (2.3)	37	0.9 (2.5)		-0.40 [-1.51, 0.71]
6 Physical arousal						
Michelson 2002	35	0.9 (2.3)	37	0.8 (2.1)		0.10 [-0.92, 1.12]
7 Orgasm						
Michelson 2002	35	0.5 (2.1)	37	1.2 (2)		-0.70 [-1.65, 0.25]
8 Pleasure/enjoyment						
Michelson 2002	35	0.7 (1.9)	37	1 (2.2)		-0.30 [-1.25, 0.65]
9 Discomfort						
Michelson 2002	35	1.1 (2.1)	37	0.7 (2)		0.40 [-0.55, 1.35]



Analysis 11.3. Comparison 11 Mirtazapine vs placebo, Outcome 3 Endpoint modified Kinsey Structured Interview.

Review: Strategies for managing sexual dysfunction induced by antidepressant medication

Comparison: 11 Mirtazapine vs placebo

Outcome: 3 Endpoint modified Kinsey Structured Interview

Study or subgroup	Mirtazapine N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Sexual satisfaction							
Michelson 2002	36	3.2 (0.9)	39	2.6 (0.9)		100.0 %	0.60 [0.19, 1.01]
Total (95% CI)	**36**		**39**			**100.0 %**	**0.60 [0.19, 1.01]**

Heterogeneity: not applicable

Test for overall effect: Z = 2.88 (P = 0.0039)

Test for subgroup differences: Not applicable

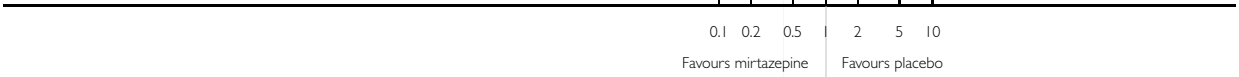
Analysis 11.4. Comparison 11 Mirtazapine vs placebo, Outcome 4 Dropouts.

Review: Strategies for managing sexual dysfunction induced by antidepressant medication

Comparison: 11 Mirtazapine vs placebo

Outcome: 4 Dropouts

Study or subgroup	Mirtazapine n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Attributed to adverse effects				
Michelson 2000	12/36	2/39		6.50 [1.56, 27.07]



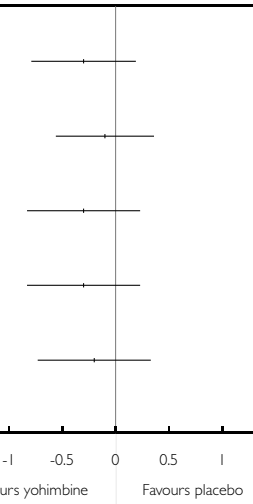
Analysis 12.1. Comparison 12 Yohimbine vs placebo, Outcome 1 Change in patient rated assessment of sexual function.

Review: Strategies for managing sexual dysfunction induced by antidepressant medication

Comparison: 12 Yohimbine vs placebo

Outcome: 1 Change in patient rated assessment of sexual function

Study or subgroup	Yohimbine N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Overall satisfaction						
Michelson 2002	35	-1.1 (1.2)	37	-0.8 (0.9)		-0.30 [-0.79, 0.19]
2 Sexual interest						
Michelson 2002	35	-0.8 (1)	37	-0.7 (1)		-0.10 [-0.56, 0.36]
3 Psychological arousal						
Michelson 2002	35	-1.1 (1.1)	37	-0.8 (1.2)		-0.30 [-0.83, 0.23]
4 Lubrication						
Michelson 2002	35	-0.8 (1.2)	37	-0.5 (1.1)		-0.30 [-0.83, 0.23]
5 Orgasm						
Michelson 2002	35	-0.9 (1.2)	37	-0.7 (1.1)		-0.20 [-0.73, 0.33]



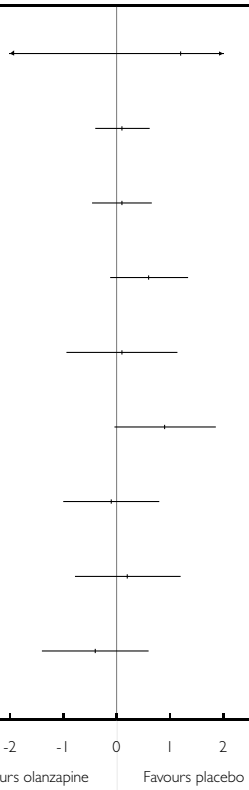
Analysis 12.2. Comparison 12 Yohimbine vs placebo, Outcome 2 Change in diary ratings (visual analogue scales).

Review: Strategies for managing sexual dysfunction induced by antidepressant medication

Comparison: 12 Yohimbine vs placebo

Outcome: 2 Change in diary ratings (visual analogue scales)

Study or subgroup	Yohimbine N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Overall sexual function						
Michelson 2002	35	6.4 (9.1)	37	5.2 (10.1)		1.20 [-3.24, 5.64]
2 Mood						
Michelson 2002	35	0.3 (1.1)	37	0.2 (1.1)		0.10 [-0.41, 0.61]
3 Energy						
Michelson 2002	35	0.4 (1.1)	37	0.3 (1.3)		0.10 [-0.46, 0.66]
4 Sexual interest						
Michelson 2002	35	1 (1.8)	37	0.4 (1.3)		0.60 [-0.13, 1.33]
5 Psychological arousal						
Michelson 2002	35	1 (2)	37	0.9 (2.5)		0.10 [-0.94, 1.14]
6 Physical arousal						
Michelson 2002	35	1.7 (2)	37	0.8 (2.1)		0.90 [-0.05, 1.85]
7 Orgasm						
Michelson 2002	35	1.1 (1.9)	37	1.2 (2)		-0.10 [-1.00, 0.80]
8 Pleasure/enjoyment						
Michelson 2002	35	1.2 (2.1)	37	1 (2.2)		0.20 [-0.79, 1.19]
9 Discomfort						
Michelson 2002	35	0.3 (2.3)	37	0.7 (2)		-0.40 [-1.40, 0.60]

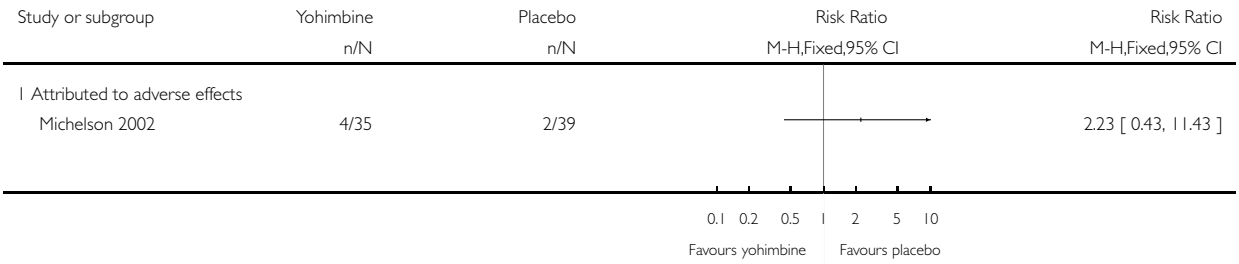


Analysis 12.3. Comparison 12 Yohimbine vs placebo, Outcome 3 Dropouts.

Review: Strategies for managing sexual dysfunction induced by antidepressant medication

Comparison: 12 Yohimbine vs placebo

Outcome: 3 Dropouts

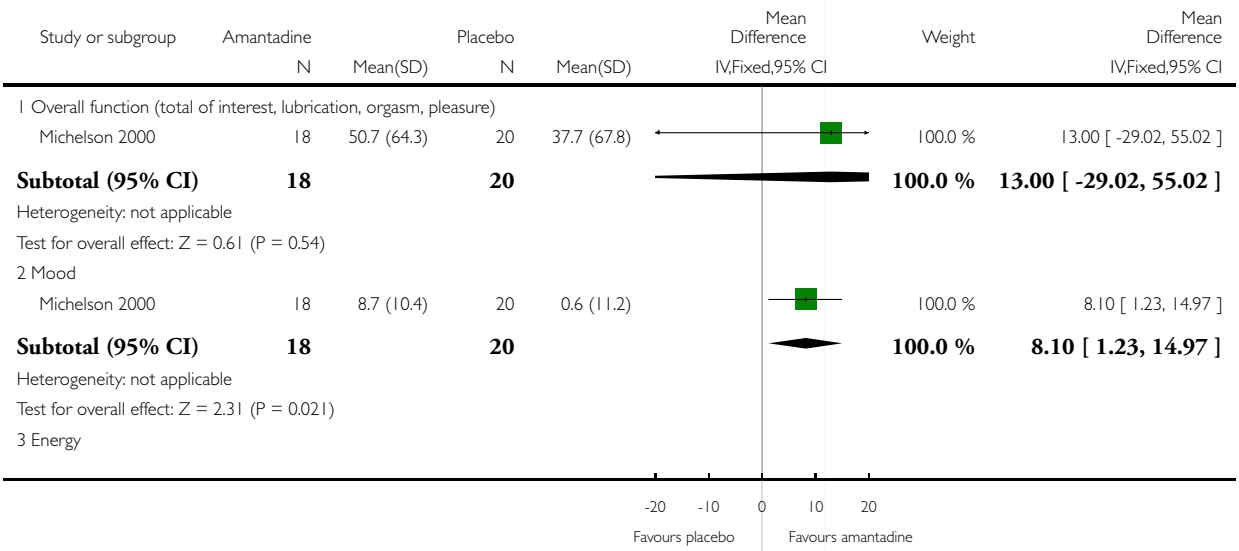


Analysis 13.1. Comparison 13 Amantadine vs placebo, Outcome 1 Change in patient-rated visual analogue scales.

Review: Strategies for managing sexual dysfunction induced by antidepressant medication

Comparison: 13 Amantadine vs placebo

Outcome: 1 Change in patient-rated visual analogue scales



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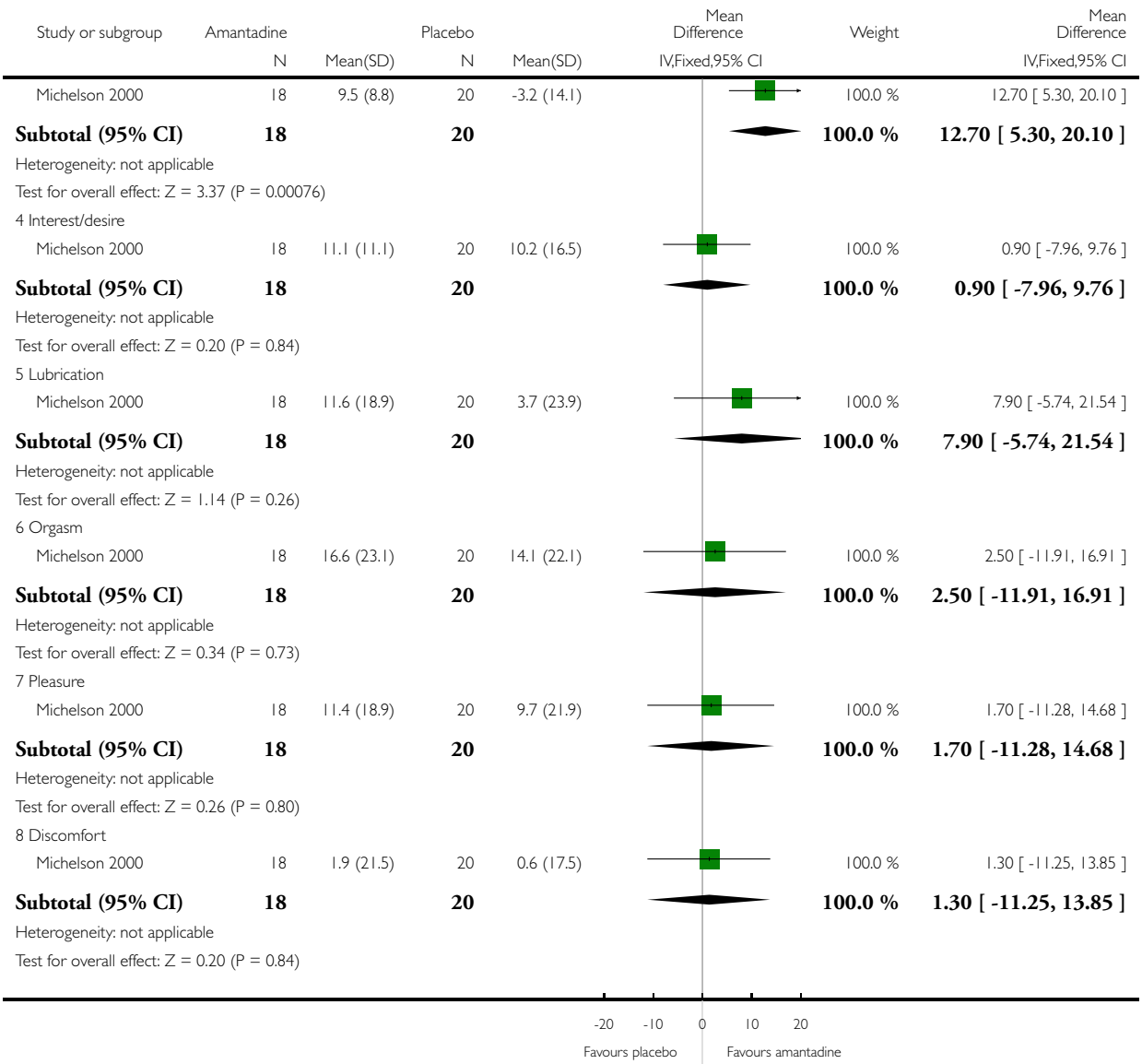


Analysis 13.2. Comparison 13 Amantadine vs placebo, Outcome 2 Dropouts.

Review: Strategies for managing sexual dysfunction induced by antidepressant medication

Comparison: 13 Amantadine vs placebo

Outcome: 2 Dropouts

Study or subgroup	amantadine n/N	placebo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Michelson 2000	1/19	1/21		1.11 [0.07, 16.47]

Analysis 14.1. Comparison 14 ephedrine vs placebo, Outcome 1 Endpoint Brief Index of Sexual Functioning for Women (BISF-W).

Review: Strategies for managing sexual dysfunction induced by antidepressant medication

Comparison: 14 ephedrine vs placebo

Outcome: 1 Endpoint Brief Index of Sexual Functioning for Women (BISF-W)

Study or subgroup	Ephedrine N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Sexual desire						
Meston 2004	19	1.79 (0.78)	19	1.95 (0.78)		-0.16 [-0.66, 0.34]
2 Sexual arousability						
Meston 2004	19	1.21 (0.78)	19	1.37 (0.78)		-0.16 [-0.66, 0.34]
3 Lack of vaginal lubrication						
Meston 2004	19	1.36 (1.26)	19	1.44 (1.48)		-0.08 [-0.95, 0.79]
4 Orgasm ability						
Meston 2004	19	1.29 (0.83)	19	1.39 (0.61)		-0.10 [-0.56, 0.36]
5 Orgasm intensity/pleasure						
Meston 2004	19	1.25 (0.83)	19	1.39 (0.74)		-0.14 [-0.64, 0.36]
6 Sexual dissatisfaction						
Meston 2004	19	1.91 (0.83)	19	1.86 (0.87)		0.05 [-0.49, 0.59]

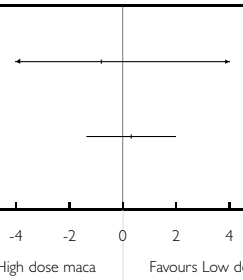
Analysis 15.1. Comparison 15 Maca root: high vs low dose, Outcome 1 Endpoint Arizona Sexual Experiences Scale (ASEX) score.

Review: Strategies for managing sexual dysfunction induced by antidepressant medication

Comparison: 15 Maca root: high vs low dose

Outcome: 1 Endpoint Arizona Sexual Experiences Scale (ASEX) score

Study or subgroup	High dose maca		Low dose maca root		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI	IV,Fixed,95% CI
1 Total score						
Dording 2008	9	16.9 (6.2)	7	17.7 (5.4)		-0.80 [-6.49, 4.89]
2 Question 1: Sexual desire						
Dording 2008	9	3.7 (1.7)	7	3.4 (1.7)		0.30 [-1.38, 1.98]



Analysis 15.2. Comparison 15 Maca root: high vs low dose, Outcome 2 Endpoint MGH-SFQ.

Review: Strategies for managing sexual dysfunction induced by antidepressant medication

Comparison: 15 Maca root: high vs low dose

Outcome: 2 Endpoint MGH-SFQ

Study or subgroup	High dose maca N	Mean(SD)	Low dose maca root N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Total score						
Dording 2008	9	17 (5.7)	7	19 (5.8)		-2.00 [-7.69, 3.69]
2 Item a: Sexual desire						
Dording 2008	9	3.3 (1.3)	7	3.4 (1.7)		-0.10 [-1.62, 1.42]

Analysis 15.3. Comparison 15 Maca root: high vs low dose, Outcome 3 Dropouts.

Review: Strategies for managing sexual dysfunction induced by antidepressant medication

Comparison: 15 Maca root: high vs low dose

Outcome: 3 Dropouts

Study or subgroup	High dose maca n/N	Low dose maca root n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Dording 2008	6/10	4/10		100.0 %	1.50 [0.60, 3.74]
Total (95% CI)	**10**	**10**		**100.0 %**	**1.50 [0.60, 3.74]**

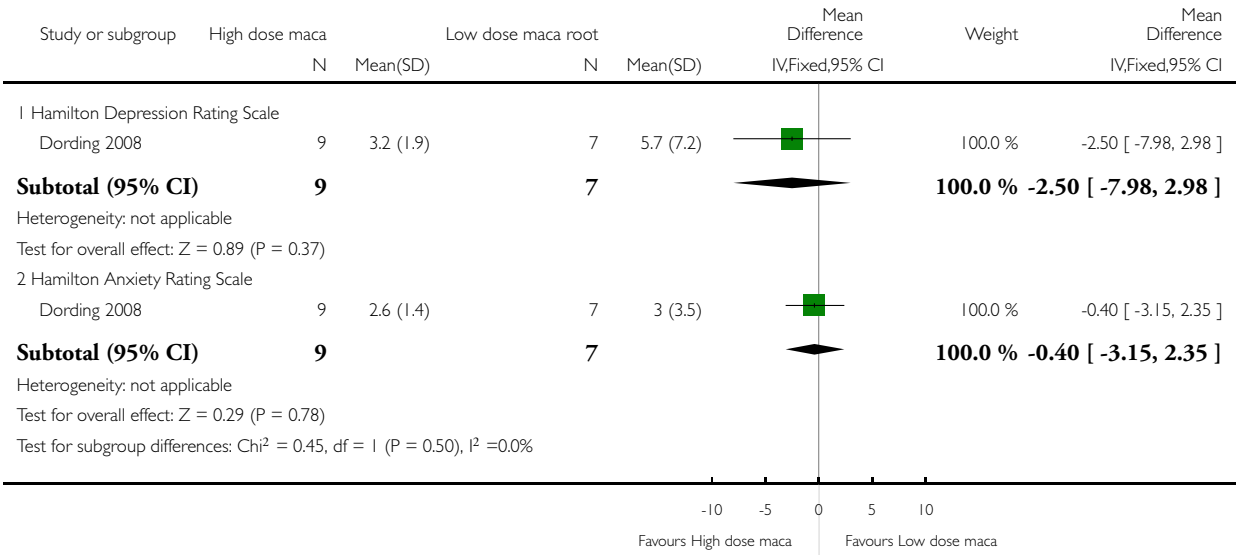
Total events: 6 (High dose maca), 4 (Low dose maca root)
Heterogeneity: not applicable
Test for overall effect: Z = 0.87 (P = 0.38)
Test for subgroup differences: Not applicable

Analysis 15.4. Comparison 15 Maca root: high vs low dose, Outcome 4 Endpoint ratings of psychiatric symptoms.

Review: Strategies for managing sexual dysfunction induced by antidepressant medication

Comparison: 15 Maca root: high vs low dose

Outcome: 4 Endpoint ratings of psychiatric symptoms



APPENDICES

Appendix 1. CCDANCTR-References Register

Sexual dysfunction		
1.	Free-text:	((sex* and (disorder* or disturb* or dysfunction* or function or "side effect*" or "adverse effect*" or "adverse event*")) or (sex* and (desire or thoughts or excitement)) or arous* or ejaculat* or erectile or erection* or impoten* or orgasm* or anorgasm* or hyperorgasm* or libido or hyposexual* or psychosexual)
Antidepressants		

(*Continued*)

2.	Free-text:	(antidepress* or anti-depress* or "anti depress*" or MAOI* or "monoamine oxidase inhibit*" or ((serotonin or norepinephrine or noradrenaline or neurotransmitt* or dopamine*) and (uptake or reuptake or re-uptake)) or SSRI* or SNRI* or TCA* or tricyclic* or tetracyclic* or heterocyclic* or pharmacotherap*)
3.	Free-text:	(Agomelatine or Alnespirone or Amoxapine or Amfebutamone or Amiflamine or Amineptine or Amitriptylin* or Amitriptylinoxide or Amoxapine or Aripiprazole or Atomoxetine or Tomoxetine or Befloxatone or Benactyzine or Binospirone or Brofaromine or Bupropion or Butriptylin* or Cianopramine or Cilobamine or Cimoxatone or Citalopram or (Chlorimipramin* or Clomipramin* or Chlomipramin* or Clorimipramine) or Clorgyline or Clovoxamine or (CX157 or Tyrima) or Dapoxetine or Deanol or Dibenzepin or Demexiptilin* or Deprenyl or Desipramine or Desvenlafaxine or Dibenzepin or Dimetacrin* or (Dosulepin or Dothiepin) or Doxepin or Duloxetine or DVS-233 or Enilospirone or Eptapirone or Escitalopram or Etoperidone or Femoxetine or Fluotracen or Fluoxetine or Furazolidone or Fluvoxamine or Harmaline or Harmine or Hyperforin or (Hypericum or (John* and Wort) or "WS 5570" or "WS 5572" or "LI 160" or LoHyp-57) or Idazoxan or Imipramin* or Iprindole or Iproniazid* or Ipsapirone or Imipraminoxide or Isocarboxazid* or Lesopitron or Levomilnacipran or Lithium or Lofepramin* or ("Lu AA21004" or Vortioxetine) or "Lu AA24530" or LY2216684 or Maprotiline or Medifoxamine or Melitracen or Metapramine or Methylphenidate or Mianserin or Milnacipran or Minaprine or Mirtazapine or Moclobemide or Nefazodone or Nialamide or Nitroxazepine or Nomifensine or Nortriptyline or Noxiptilin* or Opipramol or Paroxetine or Phenelzine or Pipofezin* or Piribedil or Pirlindole or Pivagabine or Pizotyline or Propizepine or (Protriptylin* or Pertofrane) or Quinupramine or Quipazine or Reboxetine or Ritanserin or Rolipram or Scopolamine or Selegiline or Sertraline or (Setiptiline or Teciptiline) or Tandospirone or Tetrindole or Thiazesim or Thozalinone or Tianeptin* or Toloxatone or Tranylcypromine or Trazodone or Trimipramine or 5-Hydroxytryptophan or 5-HT or Tryptophan or Hydroxytryptophan or Venlafaxine or Viloxazine or Vilazodone or Viqualine or Zalospirone or Zimeldine)
4.	Free-text:	(Alaproclate or Caroxazone or Diclofensine or Fenfluramine or Fluparoxan or Norfenfluramine or Pheniprazine)
5.	Keywords:	(depress* and "drug therap*")
6.		or/2-5
7.		(1 and 6)

Appendix 2. CENTRAL, CINAHL, EMBASE, MEDLINE, PsycINFO: original search strategy

The Cochrane Central Register of Controlled Trials (CENTRAL Issue 2, 2004) was searched using the following search terms:
#1(sexual* and dysfunction*)
#2 psychosexual
#3 orgasm*
#4 impoten*
#5 erecti*
#6 priapism
#7 libido

#8 frigid*
#9 vaginism*
#10 lubricat*
#11 dyspareun*
#12 anorgasm*
#13 hyperorgasm*
#14 (hypoactive and (sexual and desire)
#15 (sexual* and unresponsive*)
#16 (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15)
#17 sr-depressn
#18 (#16 not #17).

CINAHL (1982-March Week 4 2004) was searched with the following terms:

1 exp Dyspareunia/
2 exp Penile erection/
3 exp orgasm/
4 priap$.mp. [mp=title, cinahl subject heading, abstract, instrumentation]
5 lubricat$.mp. [mp=title, cinahl subject heading, abstract, instrumentation]
6 (sexual adj dysfunct$).mp. [mp=title, cinahl subject heading, abstract, instrumentation]
7 (sexual adj problem$).mp. [mp=title, cinahl subject heading, abstract, instrumentation]
8 (sexual adj arousal).mp. [mp=title, cinahl subject heading, abstract, instrumentation]
9 (sexual adj satisf$).mp. [mp=title, cinahl subject heading, abstract, instrumentation]
10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11 exp Sexual dysfunction/
12 exp Impotence/
13 11 or 12
14 10 not 13

EMBASE (1980-2004 Week 13) was searched with the following terms:

1 exp controlled study/
2 exp clinical trial/
3 exp major clinical study/
4 exp randomized controlled trial/
5 exp double blind procedure/
6 exp clinical article/
7 random$.mp.
8 trial$.mp.
9 study.mp.
10 studi$.mp.
11 compar$.mp.
12 control$.mp.
13 follow$.mp.
14 placebo$.mp.
15 ((dingl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$ or dummy)).mp. [mp=title, abstract, heading word, trade name, manufacturer name]
16 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17 (animal or non-human).mp.

18 human.mp.
19 17 not 18
20 16 not 19
21 exp Dyspareunia/
22 exp Priapism/
23 exp Libido/
24 exp orgasm/
25 exp penis erection/
26 lubricat$.mp. [mp=title, abstract, heading word, trade name, manufacturer name]
27 (sexual adj dysfunct$).mp. [mp=title, abstract, heading word, trade name, manufacturer name]
28 (sexual adj problem$).mp. [mp=title, abstract, heading word, trade name, manufacturer name]
29 (sexual adj arousal).mp. [mp=title, abstract, heading word, trade name, manufacturer name]
30 (sexual adj satisf$).mp. [mp=title, abstract, heading word, trade name, manufacturer name]
31 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
32 exp Sexual dysfunction/
33 exp Impotence/
34 32 or 33
35 31 not 34
36 20 and 35

Medline (1966-June Week 4 2004) was searched with the following terms:

1 exp Dyspareunia/
2 exp Priapism/
3 libido.mp. [mp=title, abstract, registry number word, mesh subject heading]
4 orgasm$.mp. [mp=title, abstract, registry number word, mesh subject heading]
5 erecti$.mp. [mp=title, abstract, registry number word, mesh subject heading]
6 lubricat$.mp. [mp=title, abstract, registry number word, mesh subject heading]
7 (sexual adj dysfunct$).mp. [mp=title, abstract, registry number word, mesh subject heading]
8 (sexual adj problem$).mp. [mp=title, abstract, registry number word, mesh subject heading]
9 (sexual adj arousal).mp. [mp=title, abstract, registry number word, mesh subject heading]
10 (sexual adj satisf$).mp. [mp=title, abstract, registry number word, mesh subject heading]
11 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12 exp impotence/ or exp sexual dysfunctions, psychological/
13 11 not 10
14 11 not 12
15 exp Sex disorders/
16 11 or 15
17 16 not 12
18 ("randomized controlled trial" or "controlled clinical trial").pt.
19 17 and 18

PsycINFO (1984- March Week 4 2004) was searched with the following terms:
1 exp dyspareunia/
2 exp libido/
3 exp orgasm/
4 exp "erection (penis)"/
5 lubricat$.mp. [mp=title, abstract, heading word, table of contents, key phrase identifiers]
6 (sexual adj dysfunct$).mp. [mp=title, abstract, heading word, table of contents, key phrase identifiers]
7 (sexual adj problem$).mp. [mp=title, abstract, heading word, table of contents, key phrase identifiers]
8 (sexual adj arousal).mp. [mp=title, abstract, heading word, table of contents, key phrase identifiers]
9 (sexual adj satisf$).mp. [mp=title, abstract, heading word, table of contents, key phrase identifiers]
10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11 exp impotence/
12 10 not 11

WHAT'S NEW

Last assessed as up-to-date: 1 January 2013.

Date	Event	Description
1 April 2013	New search has been performed	Methodology and search updated
1 April 2013	New citation required and conclusions have changed	Additional studies incorporated

HISTORY

Protocol first published: Issue 4, 2001

Review first published: Issue 4, 2004

Date	Event	Description
2 February 2013	New search has been performed	updated search and new trials incorporated
5 November 2008	Amended	Converted to new review format.
28 July 2004	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

For the original version of the review, LR and KH conceived the review and developed its initial design. LR, KH, and MT developed the review protocol. LR co-ordinated the protocol development. MT and LR carried out the selection of trials, data extraction, and data analysis. MT and KH carried out quality assessments. LR, MT, and KH contributed to the interpretation of results and preparation of the review manuscript. CC contributed to an unpublished update of the review performed in 2008. For the 2013 update, PBD, JL, MT performed updated literature searches, trial selection, quality assessments, data extraction and analyses. MT prepared the manuscript, co-ordinated completion of the full review and will act as guarantor.

DECLARATIONS OF INTEREST

PBD, CC, JL: None known.

KH has previously acted as a temporary consultant for Pfizer (manufacturers of sildenafil).

MT has been paid to lecture and received travel expenses from Bristol-Myers Squibb (manufacturers of buspirone) and Otsuka; his spouse is an employee of GlaxoSmithKline (manufacturers of bupropion).

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Internal sources

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- Institute of Psychiatry, King's College London, UK.

External sources

- National Institute for Health Research, UK.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

This updated review incorporates a revised, more inclusive, search strategy and updated quality assessment methodology including use of the Cochrane risk of bias tool.

INDEX TERMS

Medical Subject Headings (MeSH)

Antidepressive Agents [*adverse effects]; Randomized Controlled Trials as Topic; Sexual Dysfunction, Physiological [*chemically induced; *therapy]

MeSH check words

Female; Humans; Male